From DEPARTMENT OF WOMEN'S AND CHILDREN'S HEALTH
Karolinska Institutet, Stockholm, Sweden

UNPROVOKED SEIZURES IN CHILDREN: INCIDENCE, NEURODEVELOPMENTAL COMORBIDITIES AND TREATMENT

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Stockholm 2019

Published by Karolinska Institutet.
Printed by Eprint AB

ISBN **978-91-7831-537-6**

Unprovoked Seizures in Children: Incidence, Neurodevelopmental Comorbidities and Treatment
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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‘Men i Katthultsjön bland vita näckrosor simmade Emil och Alfred omkring i det svala vattnet, och på himlen satt julimånen röd som en lykta och lyste för dem. ”Du och jag, Alfred”, sa Emil. ”Ja, du och jag, Emil”, sa Alfred. ”Tror jag det!”’

- *Ur Nya hyss av Emil i Lönneberga, av Astrid Lindgren*

To my Rascals, I will love You always and forever.

ABSTRACT

Epilepsy is considered to be the neurological disease that gives the largest burden of disease in children. It is a heterogeneous disease with very diverse consequences in the lives of the patient. Comorbidities with other neurological, as well as developmental, and psychiatric, diseases are common.

The aim of this thesis was to describe the incidence of epileptic seizures in children and adults, the prevalence of neurodevelopmental comorbidities and cerebral palsy (CP) in children with seizures, and the implication of these comorbidities on the seizure prognosis in children.

The thesis was based on data from the Stockholm Incidence Registry of Epilepsy (SIRE). Medical records of all inhabitants of a designated area in northern Stockholm, seeking medical assistance for an unprovoked seizure between September 1st 2001 and December 31st 2006 were screened. Those who were diagnosed with an epileptic seizure for the first time (index seizure) during that timeframe were included in the Stockholm Incidence Registry of Epilepsy (SIRE). Medical records from before, and up until six months after, the index seizure were assessed regarding seizure type, epilepsy type and aetiology. The comorbidities developmental delay, speech/language and learning difficulties, intellectual disability, CP, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and unspecified psychiatric disorders were given special attention. The medical records of the children in SIRE were also assessed two years after the index seizure for information regarding the neurodevelopmental comorbidities and CP, treatment with antiepileptic drugs (AEDs) and seizure remission. SIRE was also linked to the Swedish Prescribed Drug Registry (SPDR) for the period 2005–2014, where information of the use of AEDs, neuroleptics, antidepressants and medication for ADHD was retrieved.

Study I included all patients (of all ages, 56% men) included in SIRE between Sept 1st 2001 and Aug 31st 2004 (N=1015). The incidence of a first unprovoked seizure was 35/100,000 person years (95% CI: 33.3–37.6). Seizure classification was possible in 72%, with generalized seizure debut only identified among those younger than 50 years old. A presumed aetiology was identified in 28% of the children (0–15 years old), in 37% of those 15 to 69 years, and in 64% of those over 70 years old. Stroke (11%) and brain tumours (9%) were the most common causes (primarily in adults). Neurological deficits from births were identified in 10% of the patients. The methodology of SIRE seemed effective regarding identification of seizure patients.

Study II included all children (28 days up to 19 years old, 56% boys) included in SIRE between Sept 1st 2001 and Dec 31st 2006 (n=766). The seizure incidence was 67/100,000 person years overall and highest for those younger than one-year-old (204/100,000). Neurodevelopmental comorbidity or CP was found in 32% of the children, and 11% had more than one of the defined comorbidities.

Study III was based on a 2-year follow-up of children included in *Study II* (n=750 with available records). Neurodevelopmental comorbidity or CP was found in 35% (95% CI:32–38%) of the children. Remission from seizures month 13 to 24 after the index seizure, or start of treatment with AEDs, was achieved by 69% of all the children, but those with a neurodevelopmental comorbidity or CP still had seizures almost three times as often as those without a comorbidity (OR: 2.87, 95% CI:2.07–3.99).

Study IV was also based on the children in *Study II*, with a few new inclusions due to late access to medical journals (n=769). Eight years after the index seizure, 31% of all the children were still dispensed AEDs, four times more often to children with neurodevelopmental comorbidity or CP compared to those without (OR: 4.0 95% CI: 2.9–5.6). Neuroleptics, antidepressants and drugs for ADHD were dispensed to between 1-5% of the children in SIRE, this was 2–10 times more often than what was reported in the general population at the time.

In conclusion, neurodevelopmental comorbidities and CP were common among children with epileptic seizures and were present already at the time of onset of seizures. This indicating that these conditions may have a common innate cause, rather than epilepsy per se causing the neurodevelopmental deficiencies. Children with comorbidities were less likely to achieve seizures remission and also more likely to receive treatment with neuroleptics, antidepressants and medication for ADHD. The clinical implication of these findings is that children with a first unprovoked seizure should be assessed for neurodevelopmental comorbidities and CP. This since these diagnoses are more prevalent in this group and deserves attention, and since children with these comorbidities have a worse prognosis and may benefit from more careful monitoring regarding their seizures.

SVENSK SAMMANFATTNING

Cirka var tionde person i världen kommer någon gång att få ett epilepsianfall, och ungefär en tredjedel av dem kommer att utveckla epilepsi. Epilepsi är vanligast under de första levnadsåren och hos äldre. Samsjuklighet med andra neurologiska och neuropsykiatriska sjukdomar är vanligt.

Avhandlingen behandlar förekomsten av nyinsjuknande i epilepsianfall hos barn och vuxna i Norra Stockholms län och hur eventuell samsjuklighet hos dessa barn påverkar anfallsfrihet, samt framtida användande av neuroleptika, antidepressiva och läkemedel mot ADHD.

Avhandlingen baseras på data från Stockholm Incidence Registry of Epilepsy (SIRE). Patienter, utan tidigare känd anfallssjukdom, som sökte vård för ett anfall identifierades via EEG-remisser och rapporter från kliniker i upptagningsområdet, mellan 1 september 2001 och 31 december 2006. Indexanfallet definierades som det anfall som gjorde att patienten sökte vård. Sex månader efter indexanfallet samlades relevanta journalhandlingar in för baslinjesammanställningen. Om det rapporterade anfallet bedömdes som ett oprovocerat, förstagångsanfall inkluderades patienten i SIRE. Journalinformation avseende anfallstyp, epilepsityp och etiologi inhämtades. Samsjuklighet som speciellt granskades var: psykomotorisk utvecklingsförsening, tal-, språk-, och inlärningssvårigheter, ADHD, autismspektrumsjukdomar, cerebral pares, intellektuell funktionsnedsättning och annan psykiatrisk sjukdom. För barnen som inkluderats i SIRE gjordes även en journalgranskning två år efter index. Då inhämtades också information om eventuell epilepsibehandling och anfallsfrekvens. SIRE sammanfogades med information från Läkemedelsregistret kring uttag av antiepileptika (AED), antidepressiva, neuroleptika och läkemedel mot ADHD.

Studie I inkluderade alla patienter (alla åldrar, 56 % män) som inkluderats i SIRE mellan 1 september 2001 och 31 december 2004 (N=1015). Incidens för ett första oprovocerat anfall var 35/100 000 personår. Anfallsklassifikation kunde göras för 72 % av patienterna, med generaliserad anfallsdebut bara identifierad bland patienter yngre än 50 år. En trolig etiologi kunde fastställas hos 28 % av barnen (0–15 år), hos 37 % av patienterna mellan 15 och 69 år, och 64 % av de som var äldre än 70 år. De vanligaste etiologierna var stroke (11 %) och hjärntumörer (9 %), bägge framför allt diagnosticerade hos vuxna. Medfödda neurologiska avvikelser identifierades hos 10 % av patienterna. Metoden för att identifiera patienter med anfall föreföll robust.

Studie II inkluderade alla barn (28 dagar – 19 år, 56 % pojkar) som inkluderats i SIRE mellan 1 september 2001 och 31 december 2006 (n=766). Anfallsincidensen var 67/100 000 personår, högst för de yngre än ett år (204/100 000). Utvecklingsneurologisk samsjuklighet och/eller CP konstaterades hos 32 %, och 11 % av barnen hade mer än en av de definierade samsjukligheterna.

Studie III var en 2-års uppföljning av barnen i *Studie II* (n=750, med kompletta journaluppgifter). Efter 24 månader konstaterades utvecklingsneurologisk samsjuklighet

och/eller CP hos 35 % (95 % CI: 32– 38 %). De med samsjuklighet hade högre risk för fortsatta anfall månad 13–24 efter indexanfallet, eller insättande av antiepileptika. Anfallsfrihet uppnåddes under denna period hos 69 % av alla barnen, men nästan tre gånger så många av de med utvecklingsneurologisk samsjuklighet eller CP fortsatte att ha anfall, jämfört med de utan samsjuklighet (OR: 2.87, 95 % CI: 2.07–3.99).

I *Studie IV* gjordes en sammanslagning av uppgifterna för barnen i *Studie II* (n=769, på grund av några sena journalkompletteringar) med Läkemedelsregistret. Åtta år efter indexanfallet hämtade 31 % av alla barnen ut antiepileptika på apoteket, läkemedelsuttag var fyra gånger så vanligt hos barn med utvecklingsneurologisk samsjuklighet och/eller CP än hos dem utan (OR: 4.0, 95 %, CI: 2.9–5.6). Totalt hämtade 1–5 % av barnen ut läkemedel mot ADHD, antidepressiva eller neuroleptika, vilket var 2–10 gånger så ofta i relation till det rapporterade uttaget av dessa läkemedel hos den totala barnpopulationen i Stockholm under denna tidsperiod.

Studierna i avhandlingen visade sammanfattningsvis på en incidens för ett förstagångsanfall hos barn i enlighet med tidigare internationella studier och att de definierade samsjukligheterna fanns redan vid anfallsdebut. Detta talar emot att epilepsin skulle orsaka utvecklingsavvikelsen, utan i stället för att det finns en gemensam, bakomliggande orsak till sjukdomarna. Barn med samsjuklighet hade lägre sannolikhet att bli anfallsfria under månad 13–24 efter indexanfallet, och fler av dem behandlades med antiepileptika, antidepressiva, neuroleptika och läkemedel mot ADHD åtta år efter indexanfallet, jämfört med barnen utan samsjuklighet. Barn med ett förstagångsanfall bör alltså bedömas avseende neurologiska utvecklingsavvikelser och neuropsykiatriska tillstånd. Detta då diagnoserna förekommer oftare hos barn med epilepsi jämfört med barn inom normalpopulationen, och då denna samsjuklighet påverkar epilepsiprognosen.

LIST OF SIENTIFIC STUDIES

This thesis is based on the following original articles and manuscript, hereafter referred to by their Roman numerals (I-IV).

I. C. Adelöw, **E. Åndell**, P. Åmark, T. Andersson, E. Hellebro, A. Ahlbom and T. Tomson (2009).

Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE).

Epilepsia 50(5): 1094-1101.

C. Adelöw, **E. Åndell,** P. Åmark, T. Andersson, E. Hellebro, A. Ahlbom, T. Tomson. Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE) Epilepsia2009;50:1094–1101
Errata
Epilepsia, 52(8):1529,2011 doi:10.1111/j.1528-1167.2011.03249.x

II. **E. Åndell**, T. Tomson, S. Carlsson, E. Hellebro, T. Andersson, C. Adelöw and P. Åmark (2015).

The incidence of unprovoked seizures and occurrence of neurodevelopmental comorbidities in children at the time of their first epileptic seizure and during the subsequent six months.

Epilepsy Res 113: 140-150.

III. **E. Åndell**, T. Tomson, S. Carlsson, K. Tedroff and P. Åmark (2018).

Neurodevelopmental comorbidities and seizure control 24 months after a first unprovoked seizure in children.

Epilepsy Res 143: 33-40.

IV. **E. Åndell**, T. Tomson, P. Åmark, N. Pihlström, K. Tedroff, S. Carlsson

Childhood onset seizures: Long-term follow-up of antiepileptic drugs, and drugs for neuropsychiatric use.

Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
AEDs	antiepileptic drugs
ASD	autism spectrum disorder
ATC	anatomical therapeutic chemical
CI	confidence interval
CP	cerebral palsy
CT	computer tomography
EEG	electroencephalogram
ESSENCE	early symptomatic syndromes eliciting neurodevelopmental clinical examinations
HR	hazard ratio
ICD-10	international classification of disease -10
ID	intellectual disability
ILAE	international league against epilepsia
IQ	intelligence quotient
MRI	magnet resonance imaging
NMDA	n-methyl-d-aspartate
OR	odds ratios
RCT	randomized controlled trials
SES	socioeconomic status
SIRE	Stockholm incidence registry of epilepsy
SNRI	serotonin–norepinephrine reuptake inhibitors
SPDR	Swedish prescribed drug register
SSRI	selective serotonin reuptake inhibitor
WHO	world health organization

1 INTRODUCTION

'I do not believe that the Sacred Disease is any more divine than any other disease but, on the contrary, has specific characteristics and a definite cause…The brain is the seat of this disease, as it is of other very violent diseases'.
- Hippocrates, 'On the Sacred Disease' (400 BC).

In spite of Hippocrates' insightful description of this ancient disorder, the history of epilepsy has been described as '4000 years of ignorance, superstition and stigma, followed by 100 years of knowledge, superstition and stigma' (Kale, 1997). Among neurological disorders (excluding stroke) epilepsy is considered number three regarding burden of disease worldwide in all ages (2016) and number one in children and young adults (2017). Epilepsy affects both sexes, all ages, all races and all socioeconomic groups, although epilepsy is more common among adults in low socioeconomic groups, where risk factors of epilepsy are also more common (Beghi and Hesdorffer, 2014; Hesdorffer et al., 2005). Even though almost ten percent of a population will experience a seizure during their lifetime, and more than a third of them will develop epilepsy (Gavvala and Schuele, 2016), there are still a lot of misconceptions in society about epilepsy. Epilepsy is a disease which comes with restrictions regarding driving and recommendations about career choice and leisure activities due to the unpredictable seizures, which contradict many of societies demand for self-fulfilment and planning of one's future. In some cultures, the thought of the disease being a punishment for sins or bewitchment still exists (Walker and Pinikahana, 2009). These cultural burdens, together with the consequences of the actual seizures, treatments, and comorbidities, are some of the challenges for a person with epilepsy.

Epidemiological studies are important to assess the burden of a disease, to find risk factors and causes, to identify prognostic considerations and to allocate appropriate health-care means. Epidemiology in epilepsy, is complicated since it is a heterogeneous disease with diverse consequences and comorbidities, and there is no single test to confirm the diagnosis. New knowledge has led to recently updated classifications regarding epilepsy, with the intention of making communication more precise and in that way facilitate progress both in clinical and research settings.

The main focus of the thesis is on the incidence of epilepsy and the prevalence of neurodevelopmental disorders and CP in children with seizures, and the impact of these comorbidities on the prognosis of children afflicted with epileptic seizures. This knowledge can provide prognostic information to patients and be of use for preventive measures and treatment decisions.

2 BACKGROUND

2.1 EPILEPSY

More is known about epilepsy now than when it was called the Sacred Disease at the time of Hippocrates, but there is still more knowledge to find and knowledge to be shared. To facilitate the research, and to help with the distribution of knowledge regarding epilepsy, the international professional organisation, the International League Against Epilepsia (ILAE), has published definitions and classifications which have been updated from time to time based on emerging data.

According to the definition, epilepsy requires at least one epileptic seizure. *Epileptic seizures* are due to excessive, abnormal or synchronous signalling, or depolarisation, in the brain cells. This cellular action results in a sudden and temporary change in the person, with involuntary movements or abnormal experiences such as shift of awareness, a sensory event or an autonomic phenomenon, observed by the patient or a witness (Fisher et al., 2017b; Fisher et al., 2005). Single unprovoked epileptic seizures, or a cluster of seizures appearing within 24 hours, or an episode of status epilepticus are defined as one seizure (Commission, 1993). Epileptic seizures start in the cerebral cortex, and all kinds of damage to the cortex increase the risk of lowering the threshold for seizures and cause epilepsy. Acute events such as head trauma, stroke and acute metabolic disease can give rise to seizures. Since these provoking events are temporary and the risk of seizures is small without the specific event, these seizures are not defined as epileptic, but are called ‘acute symptomatic seizures’. However, some of these medical events can result in lasting injuries, and in that way be risk factors for a later (months-years) diagnosis of epilepsy. Reflex seizures, which are another kind of seizure, are also dependent on specific, transient circumstances (e.g. photo stimuli) they are included in epilepsy since this is an enduring susceptibility to seizures. There are seizure imitators, such as vasovagal syncope, hypnagogic jerks, panic attacks, movement disorders and daydreaming, why the clinician has to ask for a detailed description of the event. To conclude; epileptic seizures are unprovoked, they are transient with a start and a finish, they have a clinical manifestation, and originate from an abnormal, enhanced synchronicity in the cells of the cortex.

Epilepsy is defined as a lasting elevated susceptibility to generate these unprovoked seizures. The definition now also includes the neurobiological, cognitive, psychological and social consequences/aspects of the disease. In a clinical setting, this means that epilepsy is, at least one unprovoked seizure and a high risk of recurrent unprovoked seizures within ten years, or two seizures more than 24 hours apart, or the make-up of an epilepsy syndrome or reflex epilepsy (Fisher et al., 2014). A high risk of recurrent seizures is considered to be at least 60%, since that is the general risk of further seizures after two seizures. Some known risk factors for a second seizure are (without automatically qualifying the patient for a diagnosis of epilepsy); if the first seizure was nocturnal, if epileptiform activity was seen on the electroencephalogram (EEG), if the computer tomography (CT) or magnetic resonance

imaging (MRI) was abnormal or if the patient had had a previous brain injury or disease (Krumholz et al., 2015). The previous definition of epilepsy (which is used in many population-based studies of epilepsy epidemiology) was at least two unprovoked seizures more than 24 hours apart (Commission, 1993). This is still the default definition if information, or lack of information, about the seizure makes evaluation of the recurrence risk insecure.

The first level of classification of an unprovoked epileptic seizure is to decide on the *seizure type*. Using the clinical symptoms and signs of the seizure (i.e. semiology) and looking for familiar patterns and sometimes with the help of EEG and brain imaging, seizures can be grouped into seizure types with a generalized, focal or unknown onset (Fisher et al., 2017a; Fisher et al., 2017b). The definitions of seizure types have also changed over time. The focus is now on whether brain networks limited to one hemisphere, or both, are involved in the seizure. *Generalized seizures* do not always include the entire cortex but they rapidly engage networks in both hemispheres. Generalized seizures are divided into motor or non-motor (absence) seizures, and then further into smaller entities such as tonic-clonic, myoclonic, epileptic spasms. *Focal seizures*, on the other hand, are initiated from one hemisphere. The seizures can be very localised, or spread across large parts of the cortex (Berg et al., 2010). A focal seizure can consequently show 'bilateral activity' in an EEG. Focal seizures can also be motor and non-motor seizures. If the patient is unresponsive during all, or a part of, the seizure it is labelled as 'impaired awareness'. A focal seizure can also be 'focal to bilateral tonic-clonic' (earlier called; secondary generalized seizure).

The next level of classification is the *epilepsy type*. Some epilepsies consist of multiple seizure types. The semiology of the seizures, together with the EEG findings provide the epilepsy type. The categories are focal, generalized, combined focal and generalized or unknown. When the EEG is normal (or inconclusive), additional seizure types or family history can give away the epilepsy type (i.e. generalized tonic-clonic seizures with a normal EEG in combination with myoclonic jerks, supports a generalized epilepsy). Patients with both generalized and focal seizures now belong to the category called 'Combined Generalized and Focal Epilepsies'. When the information is insufficient to determine the epilepsy type as either focal or generalized the term 'Unknown' should be used (Scheffer et al., 2017).

The third level of classification is the diagnosis of the *epilepsy syndrome*. Here characteristics from the seizure (such as seizure type and triggers), the examinations (EEG and imaging features), and the patient (age at onset and remission, comorbidities etc.) can be grouped into recognised syndrome. These may have associated aetiological, prognostic and treatment

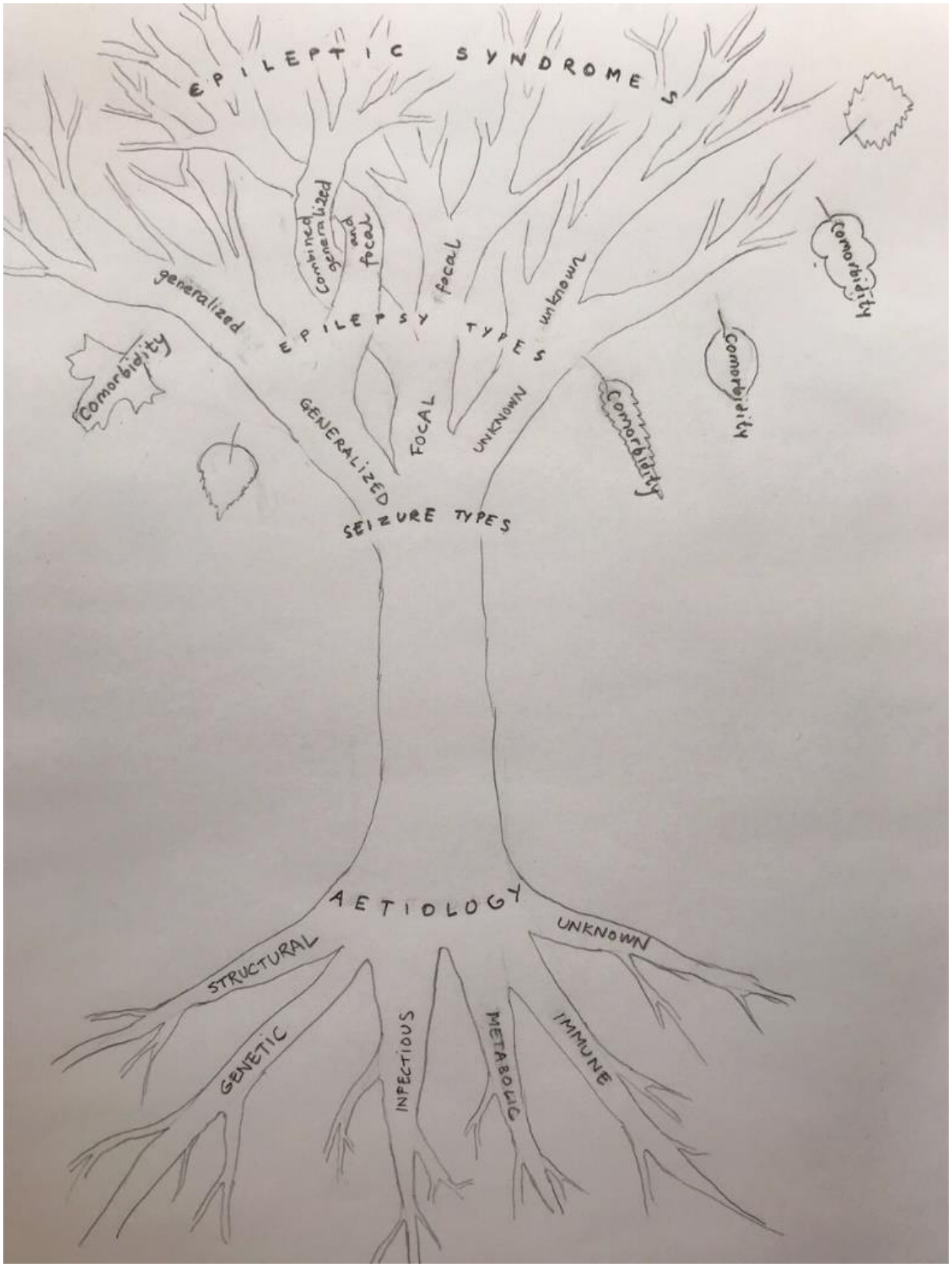

Figure 1. Classification of Epilepsy-tree, including the three levels of classification and aetiologies, by Eva Åndell Jason. The branches of the seizure types include the expanded version with generalized; motor/non-motor, focal; aware/impaired awareness, motor/non-motor, focal to bilateral clonic, unknown; motor/non-motor, unclassified. The tree is filled with different leaves depending on the presence of comorbidities.

implications. There are many well-accepted syndromes, such as childhood absence epilepsy and West syndrome, but these classifications have not been officially approved by the ILAE (Scheffer et al., 2017).

Parallel with the attempts to classify the seizure(s), epilepsy type and the epilepsy syndrome, there should be a search for the *aetiology* of the disease. An epilepsy syndrome can have more than one aetiology, and sometimes aetiology gives additional information regarding prognosis and treatment choices (Scheffer et al., 2017). The specific aetiology of epilepsy is often unknown, but the probable group of aetiology is more often possible to determine. The groupings ILAE currently recommends are: structural; genetic; infectious; immune; metabolic; and unknown (Scheffer et al., 2017). The idea is that the epilepsy results from a disorder in one of these groups, and that the core symptom of the disorder is seizures. A *structural* aetiology refers to when abnormalities on neuroimaging and electroclinical findings are the likely cause of the seizures. Even though it might be a genetic, traumatic or infectious basis to the structural abnormality, the epilepsy derives from the structural cause. The *genetic* field has evolved rapidly over the last decade. Most of the mutations are not known yet, but the genetic cause of the syndrome has been determined through twin and family studies (Sanchez-Carpintero Abad et al., 2007). A genetic aetiology in epilepsy is not always hereditary, since there are a lot of de novo mutations causing epilepsy. In some parts of the world the most common aetiology of epilepsy is an *infection*. This refers both to epilepsy as a late consequence of an earlier acute infection, a congenital infection and infections with structural correlates like tuberculosis, HIV and neurocysticercosis. Evidence of autoimmune-mediated central nervous system inflammation leading to epilepsy, such as anti-NMDA-receptor encephalitis, were recently identified, adding an *immune* group to the aetiologies. With better access to antibody testing and targeted immunotherapies this group will become increasingly important. Some *metabolic* epilepsies are acquired, but most have a genetic base. The definition in epilepsy refers to well-known metabolic defects with negative effects on the whole body. The size of the group *unknown* differs between clinical settings and countries, since the definition is that the cause is not yet known, and this is dependent on the access to specialists and medical equipment.

At the time of the large revision of definitions, the ILAE also decided to replace the term ‘benign’ with *self-limiting or pharmacoresponsive* to give a more precise and correct description of the situation for the patient.

‘Malignant’ and ‘catastrophic’ are other terms that have been removed and instead the terms *developmental and/or epileptic encephalopathy* were introduced. This pertains to epilepsies where the epileptic activity significantly adds to the developmental and behavioural impairment, resulting in more disability than was expected from the beginning (Berg et al., 2010). In epileptic encephalopathy the epileptic activity intervenes with a previously normal development, leading to cognitive, behavioural and psychiatric difficulties. If the epileptiform activity decreases, there is a possibility of improvement also of the developmental consequences. Developmental encephalopathy is when there is a developmental component

independent of the epileptic activity. The two can also be combined. There might also be other comorbidities. Outcome for this group is often poor even if the seizures stop and it is important also in this group to define the aetiology (primarily genetic) which might differ between patients with the same epilepsy (Scheffer et al., 2017).

When someone is treated for epilepsy, or had a seizure less than five years ago, that person is often defined as someone with *active epilepsy* (Commission, 1993). Epilepsy is *resolved* first if a person past the relevant age of an epilepsy syndrome that is self-limited, or after ten years of seizure-freedom without seizure medication for the last 5 years (Fisher et al., 2014). A seizure diagnosis has a great impact on a person's life, which is why a diagnosis should be given with great respect and knowledge, and always be re-evaluated once in a while, since there is no definite marker or test for the diagnosis.

The classifications in the studies of this thesis were made with the prevailing ILAE classifications at the beginning of this PhD-project. Epilepsy was defined as two or more seizures (Commission, 1981). Seizure types were then named generalized, partial (now focal), multiple seizure types or unclassified. The aetiologies were divided into symptomatic, cryptogenic or idiopathic (Commission, 1989). Symptomatic epilepsies were caused by a known brain disorder, cryptogenic by a suspected but not identified cause and idiopathic was used for specific syndromes with a known or presumed genetic cause (Commission, 1993, 1997).

2.2 EPILEPSY – EPIDEMIOLOGY

Epidemiology is the study of the distribution and determinants of a disease in a defined population. To be useful, data need to be comparable over time and across studies. This makes definitions of terminology of great importance. Epilepsy is a heterogeneous disease and its occurrence and consequences have been found to differ between countries. These discrepancies may in part be explained by methodological problems (i.e. diagnostic misclassifications, different populations, differences in definitions and difficulties in identification of patients) and socioeconomic factors (i.e. differences in etiological factors, premature mortality, stigma and treatment opportunities). To facilitate comparison between studies, guidelines for epidemiological studies in epilepsy have been written and later updated (Commission, 1993, 1997; Thurman et al., 2011). These give directions regarding preferred measurement indexes, definitions and methodological issues.

Prevalence is the proportion of individuals with a defined disease at a given time (Rothman, 2012). The time could be specific (point prevalence), a time span (period prevalence) or a full life (lifetime prevalence). *Incidence rate* is the number of new cases in a population divided by the total time at risk of that population. The incidence for a disease with a short duration (fast recovery or death) and one with long duration ('chronic') might be the same, but the prevalence will differ a lot between these two examples. *Cumulative incidence* is the new cases divided by the number of persons at risk at baseline in the same population during a defined period of time, i.e. the person's risk of developing epilepsy by the time of a specific

age. In both prevalence and incidence studies of epilepsy, specified inclusion criteria are of great importance. For incidence studies of epilepsy, it is important to define whether inclusion criteria are the diagnosis of epilepsy or onset of seizures. Incidence-based studies are primarily used to assess possible risk factors and aetiologies, to study time trends and for prognostic investigations, while prevalence-based studies primarily are important when evaluating disease burden and estimating needs of health care (Thurman et al., 2011). Ratios between incidences and prevalence's across different groups are often calculated to assess the association between different determinants and disease occurrence. Hazard ratio refers to the rate of an event (events/time unit) in one group divided by the rate of the event in the reference group. Odds ratios is the ratio between the odds of the event in the two groups (odds=probability of event(p)/probability of no event (1-p)). As with all statistics, relative measures have to be interpreted with caution, since the ratio will depend not only on the strength of association but also on the frequency of the disease in the referent population.

The point prevalence of epilepsy in the world was in a meta-analysis (197 prevalence studies) estimated to be 6.38 per 1000 (95% CI: 5,57–7.30), a little lower in high-income countries and among younger children. The overall incidence of epilepsy in the same meta-analysis (48 incidence studies) was found to be 61 per 100,000 person years (95% CI: 51–74/100,000) (Fiest et al., 2017). This would translate to 70,000 persons in Sweden having epilepsy. Young children (particularly under 1 year old) and elderly (from 65 years of age) have the highest risk of being diagnosed with epilepsy (Aaberg et al., 2017a; Forsgren et al., 2005; Olafsson et al., 2005).

The incidence of a first unprovoked epileptic seizure in children is 40–104/100,000 while 0.3–0.6% of all children in Europe and North America have epilepsy at any given time point, the prevalence seems to be higher in other areas (highest in Latin America with 7.5– 44.3/1000) (Aaberg et al., 2017a; Camfield and Camfield, 2015; Kim et al., 2016; Larsson and Eeg-Olofsson, 2006; Olafsson et al., 2005). Thus, every year at least 1000 children and 3000 adults in Sweden are diagnosed with epilepsy.

For an unbiased assessment of the incidence of unprovoked seizures and epilepsy in a population large prospective population-based studies are needed. Considering the heterogeneity of epilepsy, large numbers are needed to evaluate subgroups like seizure type and aetiology. Such studies are scarce. Few studies had used the guidelines for epidemiological studies on epilepsy from ILAE (Commission, 1993, 1997), prevailing at the time of the start of the Stockholm Incidence Registry of Epilepsy (SIRE) (see methods).

2.3 EPILEPSY IN CHILDREN

Epilepsy in children is a heterogeneous disease where the consequences are very diverse. As with any disease in children, it affects the whole family. Some parents experience a feeling of their child dying in front of their eyes at the time of the first seizure, which makes support and information to the family extremely important. The unpredictability of the disease, in

combination with the parental concern due to the disease, complicates the child's process of independence, especially for adolescents.

There are several different syndromes within the concept of epilepsy, and many of them have a childhood onset. Identification of an epilepsy syndrome gives information regarding responsiveness to antiepileptic drugs (AEDs), long-term prognosis and possible associated comorbidities. Some of the epilepsy syndromes are considered easy to treat and transient, while others demand lifelong treatment and the children will, in spite of many antiepileptic drugs, live with daily seizures. Studies using the current classification have been able to define a syndrome in about 30–40% of children with epilepsy (Aaberg et al., 2017b; Wirrell et al., 2011).

Seizure types in children seem to alter distribution with the age of seizure onset, but focal seizures are predominant in all age groups. Seizures are more often described as unclassified in younger children, and in these age groups multiple seizure types are found more often as well. Spasms were only seen in those younger than two years old (Aaberg et al., 2017b).

The aetiology of epilepsy in children is more often unknown, and has a different pattern of known causes than epilepsy in adults (Dahl-Hansen et al., 2019). The aetiology also varies between different age groups during childhood. A large population-based cohort study found a specific aetiology in one third of the children. The most common, known aetiologies, found were 'genetic' (known or presumed) and 'structural'. Children with seizure onset before the age of one, more often had a structural-metabolic cause, and less often an unknown cause compared to older children (Aaberg et al., 2017b).

Febrile seizures appears in 2–5% of children between three months and five years (Vestergaard et al., 2006). Febrile seizures are **not** epilepsy and the seizures are self-limited, around the age of five. A few of these seizures turn out to have been the first seizures in a later epilepsy syndrome, were seizures are provoked by fever (Dreier et al., 2019).

In a heterogenic disease like epilepsy in children, large studies are needed to detect different factors affecting the prognosis. It is also important to study this in a cohort with incident cases and a validated diagnosis. These limitations have been found in many previous studies.

2.3.1 Epilepsy in children – comorbidity

Epilepsy is a disease with a high presence of comorbidities. Comorbidity means that a disease coexists in patients with another disease, more often than by chance. The comorbidity might be the cause of the other disease through biological mechanisms, or a consequence of it due to a specific lifestyle reliant upon the disease or by adverse effects of the treatment of the disease or the diseases can have a common aetiology/pathogenesis. Knowledge of comorbidities is important when discussing the burden of the disease, treatment, prognosis and aetiology (Valderas et al., 2009).

The type of comorbidities differs in different ages depending on the nature of the comorbidity, and between different epileptic syndromes. Overall, though, children with epilepsy have a high burden of neurological, as well as psychiatric and other somatic comorbidities (Berg et al., 2011a; Davies et al., 2003; Gaitatzis et al., 2012; Lin et al., 2012). An elevated association between epilepsy and all the major 21 WHO disease classes has been shown and almost 80% of children with epilepsy have been found to have one or more comorbid diseases (Aaberg et al., 2016; Jennum et al., 2017). Predominant neurological disorders are headaches, cerebral palsy and neurologic congenital malformations. Neurodevelopmental or psychiatric comorbidities have been found in over 40% of the children with epilepsy with behavioural/emotional disorders, ADHD, intellectual disability, autism spectrum disorder (ASD) and unspecific neurodevelopmental delay as the most common (Aaberg et al., 2016; Reilly et al., 2014). Somewhat surprisingly somatic comorbidities are also very common in children with epilepsy, with gastrointestinal disorders, congenital non-neurological malformations and musculoskeletal disorders ranking high. A large population-based study including over 6000 children with epilepsy, reported that over 13% had one or more neurological diseases as well as a psychiatric and a somatic disease, together with their epilepsy. (Aaberg et al., 2016).

Psychiatric comorbidities have a stronger negative association with patients' quality of life than seizure frequency (Baca et al., 2011; Boylan et al., 2004; Ekinci et al., 2017). Comorbidities might also affect the treatment of seizures, through drug interactions and through complicating seizure-preventive actions such as good sleeping habits and adherence to antiepileptic drug treatment. Many of the comorbidities have an elevated risk of premature mortality, as has epilepsy, and a combination have been reported to have a negative synergetic effect on mortality (Jennum et al., 2017; Thurman et al., 2017).

Even though comorbidity is common in children with epilepsy, the heterogeneity of the disease makes the need for large cohorts to be studied in order to describe associations. Since there has been a discussion regarding the chicken and the egg of seizures and comorbidities, comorbidities need to be studied in incident seizure cases. This was previously done in a limited extent.

2.3.2 Epilepsy in children – treatment and prognosis

Epilepsy is in many cases a self-limiting disease and there are suggestions that children with epilepsy under certain circumstances could be left untreated (Arts et al., 2019). However, most children with epilepsy will start treatment with AEDs. It is known that some AEDs work better in some epileptic syndromes, but attention to the potential adverse effects of the drugs and the child's potential comorbid challenges needs to be considered as well. The most commonly reported side effects of AEDs in children are fatigue, depression and cognitive and behavioural side effects (Guilfoyle et al., 2018; Ulate-Campos and Fernandez, 2017). In spite of well-chosen AEDs, in correct doses, 20-30% of the children will still have seizures more often than once a month (Forsgren et al., 2005; Sidenvall et al., 1996). Adverse effects of the AEDs and pharmacoresistance (tried multiple AEDs without seizure remission) is more

common in children with comorbidities (Ackermann and Wilmshurst, 2015; Ulate-Campos and Fernandez, 2017; Wirrell, 2013). Children who are pharmacoresistant should be considered for alternative treatments, such as a ketogenic diet and epilepsy surgery. The long-term seizure remission in children depends on the epilepsy syndrome, comorbidities, age at seizure onset and aetiology. The majority of those with childhood-onset seizures will be seizure-free by adulthood, but those who don't achieve remission has an increased risk of death. However, epilepsy is more than seizures and other outcome measurements, such as level of education, employment and likelihood to become married are affected long after seizure remission and the termination of medical treatment (Sillanpaa et al., 1998). Different social outcomes and premature mortality, are also dependent on the child's socio-economic situation (Camfield et al., 2016; Nicoletti et al., 2009; Sillanpaa et al., 2014; Thurman et al., 2017).

Prognosis of epilepsy in relation to both neurodevelopmental comorbidities and CP was previously described to a limited extent, and the association with these comorbidities and the amount of AEDs, neuroleptics, antidepressants and drugs for ADHD dispensed to children with epilepsy was previously not assessed.

3 AIMS

3.1 OVERALL AIM

To describe the incidence of unprovoked seizures and the prevalence of neurodevelopmental comorbidities and CP in children with newly diagnosed seizures, and to increase the knowledge regarding the comorbidities' implication on seizure freedom and future drug use.

3.1.1 Specific aims

I: To determine the incidence of new onset unprovoked seizures in the Stockholm population, and to classify these seizures according to the, at the time, prevailing ILAE's guidelines.

II: To examine the incidence of unprovoked seizures in children, and the prevalence of neurodevelopmental comorbidities and/or CP at the time of a first unprovoked seizure.

III: To assess the prevalence of neurodevelopmental comorbidities and CP two years after a first unprovoked seizure, and to evaluate the overall probability of being seizure-free at that time, with or without AEDs, and in relation to neurodevelopmental comorbidities and CP.

IV: To analyse the impact of comorbidities diagnosed at the time of seizure onset regarding later use of AEDs, antidepressants, neuroleptics and drugs for ADHD.

4 THESIS AT A GLANCE

STUDY:	AIM:	METHODS:	RESULTS:	FINDINGS:
I	To determine the incidence of new onset unprovoked seizures in the Stockholm population, and to classify these seizures according to the, at the time, prevailing ILAE's guidelines.	**Study population:** Northern Stockholm (998,500 inhabitants). **Inclusion criteria for SIRE:** inhabitants of the area, seeking medical assistance for a first unprovoked seizure (index seizure), between Sept 1st 2001 and Aug 31st 2004 **Assessing:** medical records from before, and up until 6 months after, the index seizure (baseline) regarding: classification of the seizures; risk factors; and aetiology. **Statistics:** Official population numbers were used to calculate the person years. Age- and sex-specific incidence rates, and age-adjusted rates using the European Standard Population were calculated. 95% CI was calculated using the Poisson distribution.	1 015 patients (56% men and 58% with recurrent seizures at baseline) were included. *The crude incidence of a first unprovoked seizure and epilepsy was 35.4/100,000 person years (95% CI: 33.3–37.6) *Seizures were classified as: partial 62%, generalized 9.8% and unclassified 27.8%. *Presumed aetiology was present in 37.6% of the patients, with stroke (11%) and brain tumour (9%) as the most common (primarily in adults). Neurological deficits from birth was found in 10.3%.	The incidence of seizures was overall slightly lower than earlier findings, especially in the elderly, but with a similar distribution of gender, seizure type and aetiology indicating a sustainable method to identify incident cases. Seizure type and aetiology was decided on at a relatively low level, probably due to the dependence on medical records but also due to strict criteria for classification.
II	To examine the incidence of unprovoked seizures in children, and the prevalence of neurodevelopmental comorbidities and/or CP at the time of a first unprovoked seizure.	**Inclusion criteria:** Children, 28 days–18 years old, included in SIRE Sept 1st 2001 to Dec 31st 2006. **Assessing:** seizure-incidence and baseline information on classification and aetiology of the seizures, and the prevalence of neurodevelopmental comorbidity and CP. **Statistics:** Official population numbers were used to calculate the person years. Age- and sex-specific incidence rates and prevalence's were calculated. 95% CI was calculated using the Wilson score interval.	766 children included, 56% boys and mean age 9 years. *The incidence of a first unprovoked seizure and epilepsy in children was 67/100,000 person years (95% CI: 63–72). Highest in the first year of life with 204/100,000 person years. *A neurodevelopmental comorbidity or CP was found in 68% of the children (95% CI: 64–71%). More than one of the defined comorbidities was found in 1/3 of the children.	The incidence of seizures in children in Stockholm, Sweden was in accordance with other high-income countries. There was a higher prevalence of neurodevelopmental comorbidities and CP than expected in the general population already at the time of the index seizure.
III	To assess the prevalence of neurodevelopmental comorbidities and CP two years after a first unprovoked seizure, and to evaluate the overall probability of being seizure-free at that time, with or without AEDs, and in relation to neurodevelopmental comorbidities and CP.	**Patients** – see *Study II*. **Data** baseline data and 2-years data (information from baseline + 24 months following the index seizure or start of treatment with AEDs). Documentation of seizures during month 13–24 after index, or after initiation of AEDs was defined as lack of remission. **Statistics:** Associations between baseline characteristics and remission were assessed by odds ratios (OR), estimated by logistic regression (OR, 95 % CI).	750 children, 56% boys. *The comorbidities were as prevalent at baseline as at 2-years, with the same distribution. * More than 2/3 of all children were seizure-free month 13–24. * Lack of remission was almost three times as common in children with a neurodevelopmental comorbidity or CP compared to those without (OR: 2.87, 95% CI:2.07–3.99). Lack of remission with comorbidity, and treatment with AEDs, was twice as common as for those without a comorbidity with AEDs (OR: 1.9 (95% CI: 1.4–2.6).	The prevalence of neurodevelopmental comorbidities and CP remains the same the first two years of a seizure disorder, coherent with the thought that the comorbidities and the seizures have a common cause. Less children with neurodevelopmental comorbidities and CP attained remission of seizures indicating a more complex brain disorder.
IV	To analyse the impact of comorbidities diagnosed at the time of seizure onset regarding later use of AEDs, antidepressants, neuroleptics and drugs for ADHD.	**Patients and baseline data**– see *Study II*. SIRE was **linked** to the Swedish Prescribed Drug Register (SPDR) from June 2005 (start of SPDR) until Dec 2014 to identify dispensing of AEDs and ADHD medication, antidepressants and neuroleptics by use of ATC codes. **Statistics:** Associations between baseline characteristics and drugs dispensed were assessed by odds ratios (OR) estimated by logistic regression (OR, 95% CI). The association between baseline characteristics and coming off AEDs was assessed by hazard ratios (HR), estimated with cox proportional hazard regression (HR, 95% CI).	769 children (56% boys) were studied for a median of 10 years after index * Eight years after the index seizure, 31% of all the children were still dispensing AEDs, four times more often to children with neurodevelopmental comorbidity or CP compared to those without (OR: 4.0 95% CI: 2.9–5.6). * Few children received neuroleptics, antidepressants or drugs for ADHD (1–5%), more to those with a comorbidity. This was still 2–10 times more than what was dispensed in the general population.	Only 1/3 of the children used AED after 8 years and only a few received drugs for ADHD, neuroleptics or antidepressants. There was a negative association between neurodevelopmental comorbidities and particularly CP at the time of the index seizure and long-term medication with AEDs, neuroleptics and drugs for ADHD.

5 METHOD

5.1 STUDY POPULATION AND DATA COLLECTION

The Stockholm Incidence Registry of Epilepsy (SIRE) included patients of all ages who sought medical advice for, what was concluded to be, an unprovoked seizure (hereafter, the index seizure). The catchment area was an urban area, the northern part of Stockholm, with approximately 1 million inhabitants at the time of the inclusion of patients (close to 230,000 individuals younger than 19 years old). The surveillance system was up and running from September 1st 2001. Children with seizures living in the area were continued to be included until December 31st 2006.

The catchment area was served by three hospitals, but only the Karolinska University Hospital had departments of neurology, neurosurgery and paediatric neurology and there was also one central electroencephalography (EEG) laboratory reviewing all the EEGs from the area. Patients were identified through reading the EEG requests to the neurophysiological department, as well as screening of medical records at the department of Paediatric Neurology and Neurology at the Karolinska University Hospital for patients for the first time discharged with an International Classification of Disease (ICD) code of G40, G41 or R56.8. New referrals to the Neuro-oncology section and records from the paediatric emergency room records at the Karolinska University Hospital were also reviewed. A network with all neurologists, paediatricians and geriatricians, as well as nursing homes in the area was organized. They were asked to send the project coordinator a letter with the date, their own name and institution and the unique Swedish personal number of any potential case.

5.2 PROCEDURES

All relevant medical records of the patients, from before and up until six months after, the date of the potential index seizure were collected by the project coordinator. If the patient was included, this was the source of the *baseline information* about the patient. The medical records were evaluated by at least two members of a panel (neurologist T.T, neuropeadiatrician P.Å., and at the time a resident in neurology, C.A., and a resident in paediatrics E.Å.) and re-reviewed at least once in order to ascertain the consistency of application of the classifications. Patients who sought medical assistance for the first time for a first unprovoked seizure within the inclusion dates (*Study I*: September 1st 2001 through to August 31st 2004; *Study II−IV*: August 31st 2001 through to December 31st 2006), were living in the designated area, and for *Study II-IV* were younger than 19 years old (hereafter, *children*) at the time of the index seizure, were included in the cohort. Having been diagnosed with, or treated for, unprovoked seizures within five years prior to the index seizure was an exclusion criterion. For the children, medical records continued to be retrieved and reviewed until 24 months after the index seizure, or 24 months after introduction of treatment with AEDs. This information, together with the baseline data gave the *2-year data*. The time window was prolonged for those who received AEDs within two years from the index

Figure 2. Flowchart of Studies

seizure, to give room for assessment of the treatment effect. The number of AEDs tried within 24 months of initiation of treatment was counted.

In *Study IV* the child cohort was linked to The Swedish Prescribed Drug Register (SPDR) (Wettermark et al., 2007) by the unique personal number assigned to every Swedish citizen. The SPDR has been available since July 1st 2005 and the children were linked with data regarding all their dispensed drug prescriptions in Sweden up until Dec 31st 2014. The drugs are classified corresponding to the Anatomical Therapeutic Chemical (ATC) Classification System and *Study IV* analysed the ATC codes: N03A (antiepileptic drugs; AEDs); N05A (neuroleptics); N06A (antidepressants); and N06BA 01, 02, 03, 04, 09, 12 (medications licensed for the treatment of ADHD).

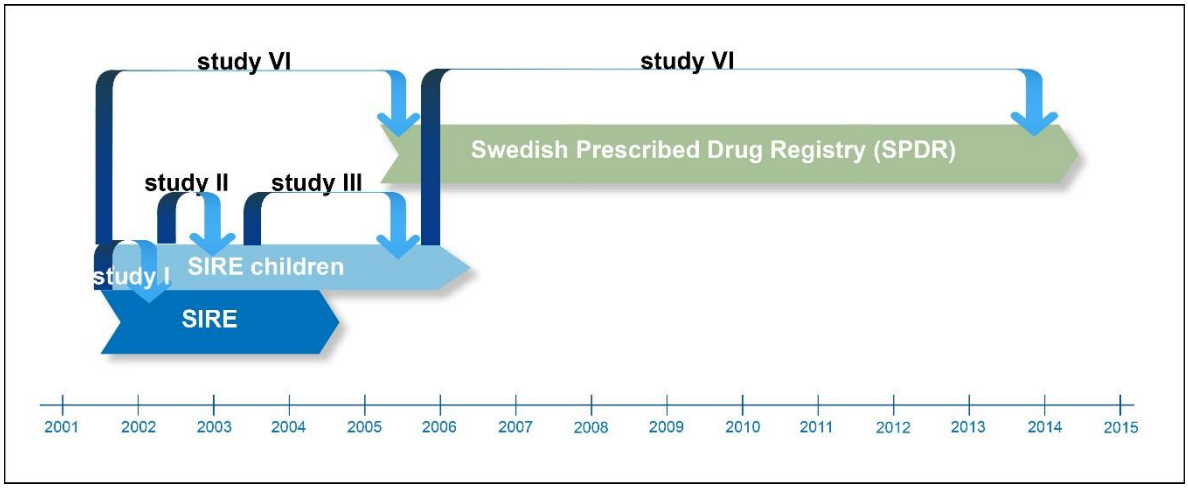

Figure 3. Timeline of Studies

5.3 DEFINITIONS

Information about the *seizure type* of the index seizure (generalized seizures, partial seizures, unclassified or multiple seizure (1981)) was retrieved on three levels within the timeframe for baseline information;

Level 1: the semiology of the index seizure,
Level 2: the semiology together with diagnostic investigations such as EEG and MRI,
Level 3: information from Level 1 and 2 + the semiology of any additional seizures.

The *probable aetiology* of the seizure was divided into the groups suggested by the ILAE at the time of the start of the registry: symptomatic (the consequence of a cerebral disease, this group was subdivided into static or progressive aetiology); cryptogenic (i.e. suspected, but not identified, underlying cause or lesion); idiopathic (i.e. specific epileptic syndromes with a presumed genetic basis); or of unknown origin. Whether there was a neurological deficit from birth was also identified (Commission, 1989, 1993, 1997). Potential *risk factors* and the most likely more *specific aetiology* (e.g. stroke, hypoxic ischaemic encephalopathies, chromosomal abnormalities) for the seizure were also assessed.

For the children, information about a priori decided *neurodevelopmental comorbidities and CP* was also extracted from the baseline information. Intellectual disability (ID), cerebral palsy (CP), autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) were defined according to corresponding ICD-10, while developmental delay, speech/language and learning difficulties and unspecified psychiatric disorder pertained to a wide variety of problems within each domain. Developmental delay was used for psychomotor delay in younger children. Speech/language and learning difficulties included children with speech disorders, dyslexia and substantial difficulties in school. Unspecified psychiatric disorder was used to describe problems for which the child had received help from a child psychiatry department. The comorbidities were classified as *suspected* if there was a distinct portrayal of the problem, but no complete investigation for a diagnosis, and as *certain* when the child had an ICD-10 diagnosis. This was done in order not to underestimate the diagnoses due to the long waiting times for work-ups present in Stockholm during this time period. In the analyses these groups were mostly combined. Since almost all of the children had visited the department of child neurology, where the physicians typically participate in neurodevelopmental and neuropsychiatric team assessments on a regular basis, a distinct problem description by them was considered credible. *ESSENCE* (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) is the acronym used for unspecific developmental problems in younger children (Gillberg, 2010). This was used in *Study II and III*. Children below six years of age, with suspected or certain problems pertaining to developmental delay, speech/language and learning difficulties, intellectual disability, ASD or ADHD, were grouped both with their individual comorbidity and in the ESSENCE group. 'Any comorbidity' corresponds to one or more suspected or certain comorbidities.

In *Study III*, potential remission of seizures was studied. This was defined as no seizures the last 12 months out of the 2-year data (13–24 months after the index seizure or initiation of treatment).

In *Study IV*, discontinuation of medication was defined as the last date of the dispensing of a group of drugs, followed by at least one year of no dispensing of the drug.

5.4 STATISTICS

Incidence rates of seizures (*Study I-II*) and prevalence of neurodevelopmental comorbidities and CP (*Study II*) were calculated with 95% CI. CIs were calculated using the Wilson score interval (Newcombe, 1998) and the Poisson distribution (Morris and Gardner, 1988). Estimates of population size used in the denominator of the incidence calculations (*Study I-II*) were based on official population numbers from Statistics Sweden (StatisticsSweden). The official size of the population in question was added at December 31st of each year studied. The total number of person years was estimated to 2,995,553 in *Study I*, where also age-adjusted incidence rates were calculated with the European Standard Population as standard population. In *Study II* the total number of person years of the children was estimated to 1,384,053.

The association between baseline characteristics and remission, as well as the number of AEDs tried among those who came to remission was assessed in *Study III*. Odds ratios (OR) with 95% confidence intervals were calculated by logistic regression for remission. Baseline characteristics studied were sex, age-group, single/recurrent seizures, type of seizures (symptomatic, cryptogenic or idiopathic), comorbidity yes/no, and type of comorbidity. The comorbidities were examined in the same model (i.e. mutually adjusted), and the ORs were adjusted for sex and age groups.

The baseline characteristics sex, single/recurrent seizures, comorbidity yes/no, and type of comorbidity were in *Study IV* analysed regarding association with treatment with AEDs, neuroleptics, antidepressants and ADHD medication four and eight years after index. Also in this study ORs and CIs were estimated by logistic regression, and comorbidities were assessed both in relation to specific comorbidities (in the same model) and any vs no comorbidity. In *Study IV* the hazard ratio (HR) of discontinuing treatment with AEDs in children who received treatment between July 1st 2005 and Dec 31st 2014 was also assessed in relation to baseline characteristics. HRs and 95% CIs were estimated by cox proportional hazard regression and the HRs were adjusted for sex and age (Model 1) and for age, sex, single/multiple seizures, comorbidity yes/no, and date of index seizure (Model 2).

Analyses in *Study I-III* were made in SAS 9.1 and 9.2 and *Study IV* in SPSS version 22.

5.5 ETHICS

The studies were approved by the Ethics Committee at Karolinska Institutet Stockholm Sweden (No 2005/979-31/4, 2008/507-31/2 and 2009/2046-31/2).

When the information from medical research can be of value to a larger group of the population, this is considered to override the privacy and integrity of individuals, according to the principle of ‘the greatest good’ (beneficence). To be part of a register can for some have very negative associations and give a feeling of discomfort. This was one of the reasons why no individual consent was obtained. It also avoids patients to being reminded of a disease or an event which some have forgotten, or never knew of, for example due to young age. The matter of voluntary participation was fulfilled, since there is information about clinical quality registers at the hospitals (waiting room areas etc.) and a person can decline to be in them, and ask to be removed from them. When linking different registers, the information was anonymised and a serial number was used and information was aggregated on group levels and were not shown on an individual level. The research questions were set a priori and all data were handled in the way described in the ethical applications and not altered in any way. The information attainable from SIRE regarding incidence, comorbidity and different kinds of prognostic information of seizures is valuable from a socio-economic, resource planning and disease management perspective. This kind of information has been scarce in large population studies, which is why the beneficence of the community in this case is of considerable value.

6 RESULTS

6.1 STUDY POPULATION

Northern Stockholm is an urban area, with a significant immigration giving a mix of ethnical origins.

Study I is based on all seizure patients included between Sept 1st 2001 and Aug 31st 2004 (N=1,015, 56% men). The incidence rates had a bimodal distribution with highest incidence among the youngest and the oldest. Recurrent seizures already at baseline was found in 58%. The seizure types were classified as focal (62%), generalized (10%) and unclassified in 28%). Aetiologies were classified as idiopathic (8%), cryptogenic (54%) and symptomatic (38%).

Study II-IV are based on the children included in SIRE Sept 1st 2001 until Dec 31st 2006. The number of children differs slightly (*Study II*: N=766, *Study III*: N=750, *Study IV*: N=769, 56% boys in all three) due to 16 patients lost to follow-up (5 died) in the 2-year data assessment, and a few new, late, inclusions in the registry (for *Study IV*). The children were between 28 days and 19 years old, median 7 years (Figure 4), and 67% had recurrent seizures at baseline. The seizure types were classified as focal (50%), generalized (21%) and unclassified in 28%). Aetiologies were classified as idiopathic (20%), cryptogenic (53%) and symptomatic (27%).

In *Study IV*, the follow-up of drugs dispensed was for a median of 10.3 years (range 0.11-13.0).

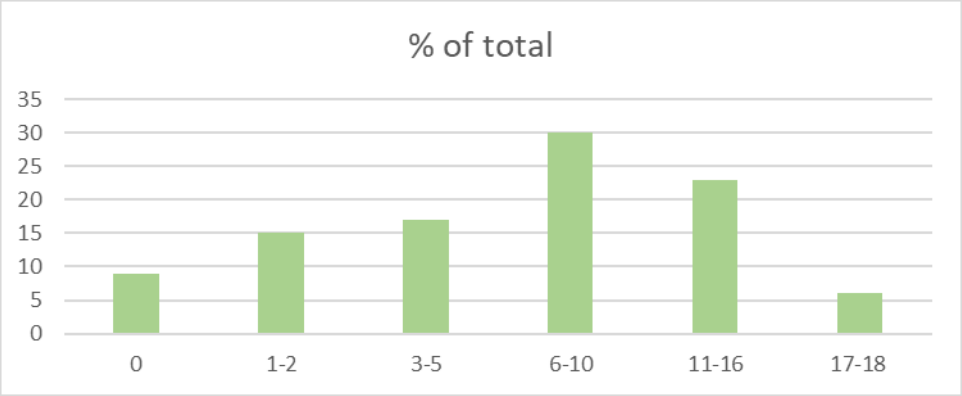

Figure 4. Distribution of the children in SIRE in different age-groups.

6.2 INCIDENCE OF SEIZURES (*STUDY I AND II*)

After three years, approximately 10,500 EEG referrals and 3,300 medical records had been screened for *Study I*, and the crude incidence rate of index seizures was found to be 35.4/100,000 person years (95% CI: 33.3–37.6) and the age-adjusted incidence rate (using the European Standard Million) (National Cancer Institute, 2008) was 39.0 per 100.000 person years. The crude incidence for males was 40.4, and 30.7 for females. The highest incidences were found among the youngest and the elderly (Figure 5). Most of the seizures (54.4%) were classified as cryptogenic, while 37.6% were symptomatic (symptomatic static 21.7% and

symptomatic progressive 15.9%) and 7.9% were classified as idiopathic. Generalized-onset seizures occurred in 100/1015 patients, all younger than 50 years old. A presumed aetiology to the seizure was found in 382/1015 (37.6%) of the patients, more often among the elderly. Stroke (115/1015, 11.3%) and brain tumour (92/1015, 9.0%) were the most common aetiologies overall, while 'other specified' (including diagnoses such as arteriovenous malformation, periventricular leucomalacia, demyelinating disease, tuberous sclerosis, mesial temporal sclerosis, brain abscess and tuberculoma) (20/382, 5.2%) and cortical malformation (16/382, 4.2%) were the most common among those younger than 15 years.

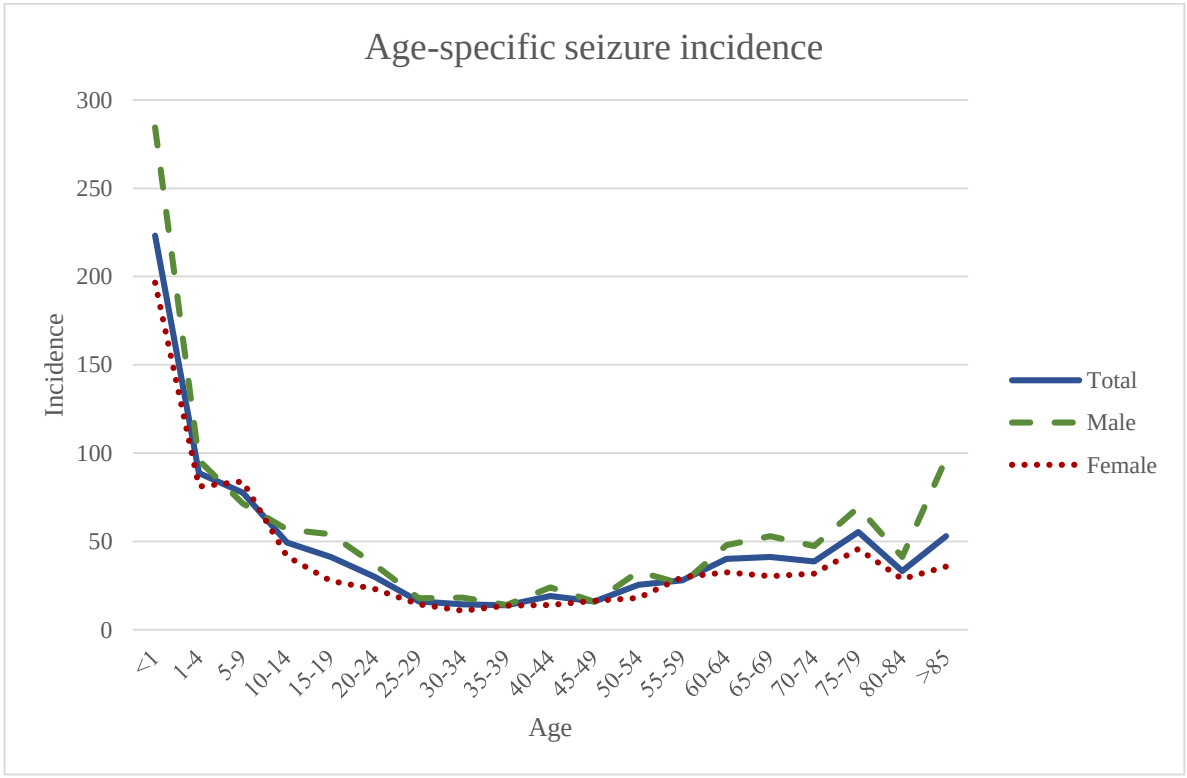

Figure 5. Incidence of epileptic seizures by age and sex, SIRE registry 2001-2004 (N=1 015).

In children 0–19 years old (*Study II*) the incidence rate of seizures was 67/100,000 (95% CI: 63-72/100,000), highest during the first year of life (204/100,000) and lowest among the 18-year-olds (30/100,000). Among 0–14 year-olds, an age-group commonly studied in children, the incidence was 74/100,000. The difference between boys and girls was small (Table 1). Half of the index seizures (385/766) were classified as focal, while 163 (21%) were generalized and 218 (28%) unclassified. The most common known aetiologies were still 'other specified' (5.0%) and cortical malformation (4.3%), but for 77.7% of those younger than 19 years old, it was not possible to determine the aetiology of the seizures. For the 247 with a comorbidity at baseline it was possible to determine the aetiology in 49.4% of the children, still with 'other specified' (11.3%) and cortical malformation (9.7%) as the most

common causes, but closely followed by hypoxic ischaemic encephalopathy (9.3%), known chromosomal abnormality (8.1%) and stroke (6.9%).

		Total					Male			Female		
Age (years)	Person years	Single unprovoked seizures (n)	Epilepsy (n)	Combined (single seizures	Incidence rate	95 % Confidence Interval	Combined (single seizures	Incidence rate	95 % Confidence Interval	Combined (single seizures	Incidence rate	95 % Confidence Interval
0	34 637	13	58	71	204	160 - 258	37	208	146 - 286	34	201	139 - 281
1	66 705	17	56	73	109	85 - 137	37	108	76 - 149	36	110	77 - 152
2	63 907	14	26	40	62	44 - 85	25	76	49 - 112	15	48	26 - 79
3	60 908	21	29	50	82	60 - 108	31	99	67 - 140	19	64	38 - 100
4	58 716	9	34	43	73	52 - 98	33	109	75 - 153	10	34	16 - 64
5	57 095	14	24	38	66	47 - 91	16	54	31 - 88	22	79	49 - 119
6	56 620	26	30	56	98	74 - 128	35	120	83 - 167	21	76	47 - 116
7	57 240	17	28	45	78	57 - 105	22	74	46 - 113	23	82	52 - 123
8	59 078	16	36	52	88	65 - 115	31	102	69 - 145	21	73	45 - 111
9	61 025	13	31	44	72	52 - 96	22	70	44 - 106	22	74	46 - 112
10	63 203	11	23	34	53	37 - 75	18	55	32 - 87	16	51	29 - 84
11	64 924	11	23	34	52	36 - 73	18	53	31 - 85	16	50	28 - 82
12	65 876	14	16	30	45	30 - 65	18	53	31 - 84	12	37	19 - 65
13	65 335	6	20	26	39	25 - 58	13	38	20 - 66	13	40	21 - 69
14	64 168	8	22	30	46	31 - 66	17	51	30 - 82	13	41	22 - 70
15	62 205	12	12	24	38	24 - 57	14	43	24 - 73	10	32	15 - 60
16	60 135	10	22	32	53	36 - 75	18	58	34 - 92	14	47	26 - 80
17	57 751	12	15	27	46	30 - 68	11	37	18 - 66	16	56	32 - 92
18	55 945	10	7	17	30	17 - 48	14	48	26 - 81	3	10	2 - 32

Table 1. Age- and sex- specific incidence rates (per 100 000 person years) of unprovoked seizures/epilepsy in Stockholm, Sweden Sept 1st 2001 through Dec 31st 2006. N=766.

6.3 NEURODEVELOPMENTAL COMORBIDITIES AND CP IN CHILDREN WITH SEIZURES (*STUDY I AND II*)

At baseline certain or suspected neurodevelopmental comorbidities or CP was found in 32% (95% CI: 29–35%) of the children (*Study II*), and at the 2-year follow-up this number was 35% (95% CI: 32–88%) (*Study III*). The comorbidities were distributed in the same way in the age groups at baseline and 2-years, but the diagnosis had changed for some individuals (e.g. from developmental delay to intellectual disability) (Figure 6). At the 2-year follow-up, 39 'new' children were diagnosed with a comorbidity, while for 16 children (12 from the ESSENCE group) the diagnosis of a comorbidity was no longer valid. The comorbidities varied with the age at seizure onset, with one of the three most frequent comorbidities, developmental delay (22%, 95% CI: 19–25%) primarily seen in the younger ages, while the other two, speech/language and learning difficulties (23%, 95% CI: 20–26%) and intellectual disability (16%, 95% CI: 13–18%) were equally present in all age groups. CP was found in 71/766 (9%) and most common among the 0–5-year-olds, while ADHD was found in 48/766 (6%), primarily among 6–16-year-olds. In the older age groups ASD and 'other psychiatric diagnosis' were most common, ASD was found in 50/766 (7%) of the children and 'other

psychiatric diagnosis' in 19/766 (2%) (Figure 6). Two out of the five comorbidities ID, CP, ASD, ADHD and other psychiatric were diagnosed in 72/766 (9.4%) of the children, and three in 14/766 (1.8%) (Figure 7). More than one comorbidity was more common in boys and among those with recurrent seizures at baseline.

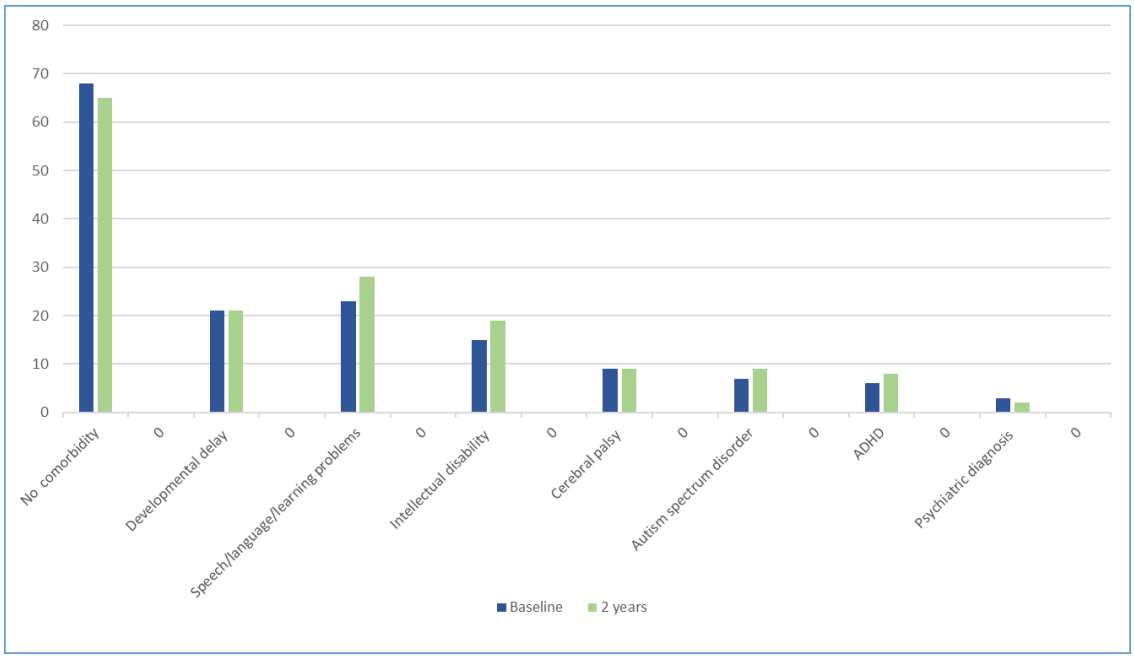

Figure 6. Prevalence (%) of comorbidities at baseline and at 2 years after the index seizure (an individual could display more than one comorbidity and a change of diagnoses from 6 to 24 months).

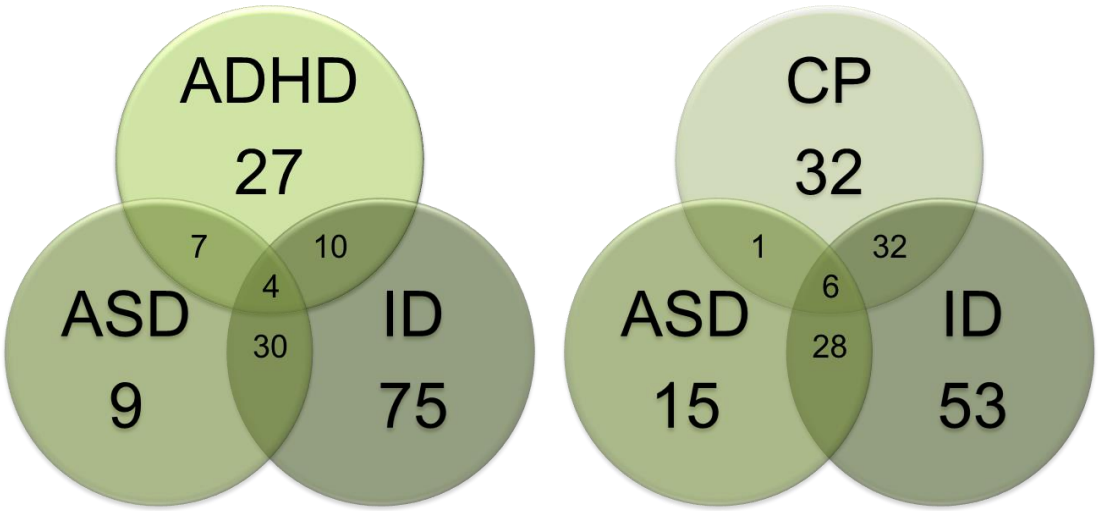

Figure 7. Combinations of comorbidities. Number of children (0-18 years) with combined comorbidities (suspected or diagnosed) at baseline. It is known that there is a high occurrence of comorbidity between epilepsy, ASD and ID, this figure shows the addition of a fourth comorbidity for 10 of the children. ID=Intellectual Disability, ADHD= Attention Deficit Hyperactivity Disorder, ASD= Autism Spectrum Disorders, CP=Cerebral Palsy. (N=766).

6.4 NEURODEVELOPMENTAL COMORBIDITIES AND CP AND SEIZURE PROGNOSIS – SHORT TERM (*STUDY III*)

Almost 70% of the children in SIRE were in remission months 13–24 after the index seizure, or after initiation of AED, boys as often as girls, but less so for those younger than eight years, compared to those 13–18 years old. Only 53% of the 239 children with comorbidities achieved this. During this time period 274/516 (55.4%) seizure-free children received AEDs (including 24/197 who had only had one seizure), while 221/234 (94.5%) of those with seizures received AEDs (Figure 8). One of the 234 children still seizing during month 13–24, had daily seizures and 10 had one to five seizures during that year. The others had six or more seizures or an unknown number of seizures. To have a comorbidity gave an odds ratio (OR) for having seizures during month 13–24 of 2.87 (95% CI: 2.07–3.99) compared to not having a comorbidity. Lack of remission with comorbidity, and treatment with AEDs, was almost twice as common as for those without a comorbidity with AEDs (OR: 1.9 (95% CI: 1.4–2.6) (Figure 8). ID, CP, ASD, ADHD and ESSENCE individually increased the risk for seizures, with CP and ESSENCE giving the highest ORs (Table 2).

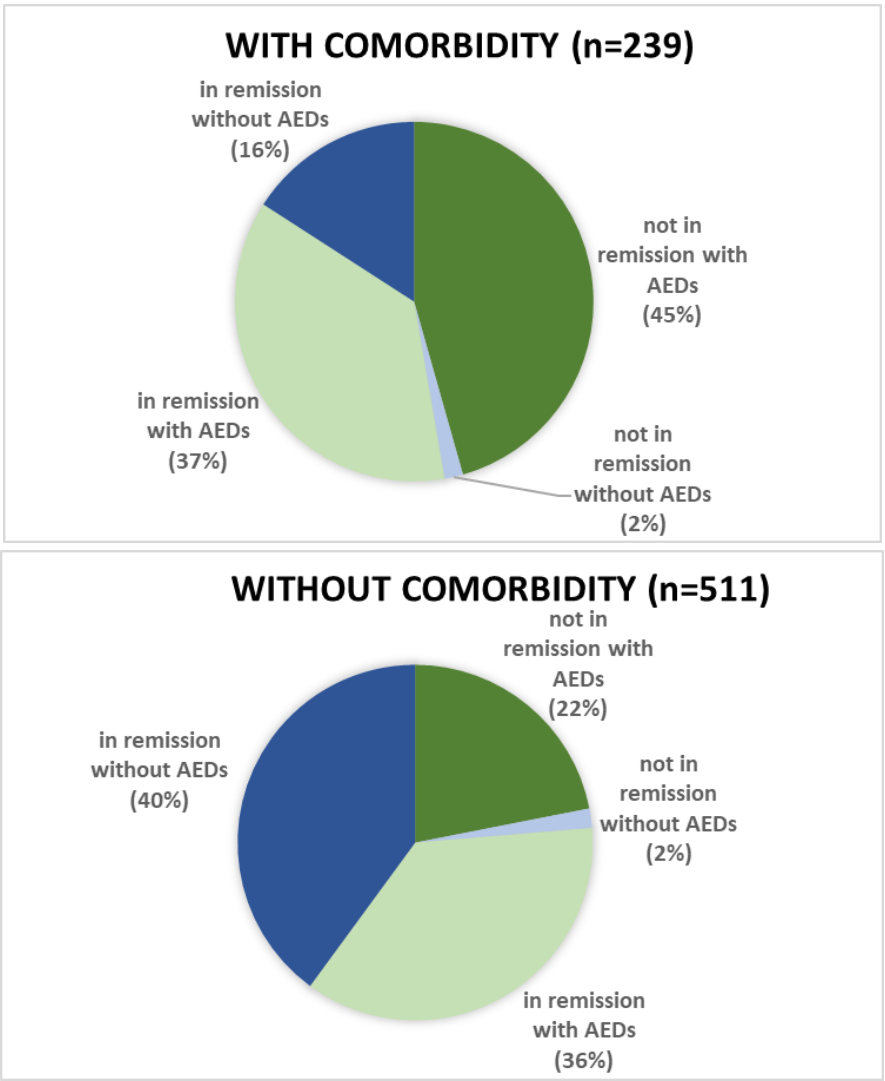

Figure 8. Seizure status months 13–24 after the index seizure/start of treatment with AEDs, in relationship to comorbidity (at baseline) and anti-epileptic treatment (AEDs). N=750.

	SEIZURES DURING MONTH 13-24			
AT BASELINE	n/total	(%)	OR	(95% CI)
Number of seizures the first 6 months				
one seizure	22/247	(9)	ref	
recurrent seizures	212/503	(42)	7.46	(4.63-12.02)
Comorbidity				
no neurodevelopmental comorbidity	121/511	(24)	ref	
neurodevelopmental comorbidity	113/239	(47)	2.87	(2.07-3.99)
developmental delay	85/159	(53)	2.42	(0.81-7.26)
speech/language/learning problems	82/169	(49)	1.30	(0.56-3.04)
intellectual disability	57/112	(51)	2.24	(1.13-4.46)
cerebral palsy	40/66	(61)	5.03	(2.81-9.01)
autism spectrum disorder	26/51	(51)	2.72	(1.38-5.36)
ADHD	24/48	(50)	3.29	(1.74-6.20)
unspecific psychiatric disorder	7/19	(37)	2.44	(0.92-6.52)
ESSENCE	60/99	(61)	5.12	(3.03-8.65)
not ESSENCE (<6-years-old)	49/205	(24)	ref	
ESSENCE	60/99	(61)	4.79	(2.86-8.03)

ref=reference for the following OR

Table 2. Odds Ratios for seizures during month 13–24 after the index seizure for all the children (N=750), in relationship to seizure frequency and comorbidity.

6.5 TREATMENT WITH ANTIEPILEPTICS – LONG TERM (*STUDY IV*)

According to the information in the SPDR, 350/769 (46%) used AEDs four years after index and 240/769 (31%) after eight years. Children with a neurodevelopmental comorbidity or CP at baseline were four times more likely to receive AEDs four and eight years after the index seizure, with the highest odds ratios for those with CP (after 4 years; 5.0, 95% CI: 2.6–9.4) and ADHD (after 4 years; 3.2, 95% CI: 1.6–6.3) compared to those without a comorbidity (Figure 9). Treatment with AEDs was as common in boys as in girls, while it was less common among those of a younger age at index, and more common for those with recurrent seizures at baseline.

Analyses of the 473 children who were dispensed AEDs between the start of SPDR (July 1st 2005) and Dec 31st 2014, showed that the probability of discontinuing the AED treatment (i.e. probable seizure remission) was similar in boys and girls and between those with single and recurrent seizures at baseline. However, children with neurodevelopmental comorbidities or CP at baseline were 60% less likely to discontinue their treatment (HR 0.4, 95% CI: 0.3–0.6, adjusted according to model 1) (Figure 10) compared to those without comorbidities (similar in-between individual comorbidities). Children older than 13 years old at index had a lower chance of discontinuing treatment with AEDs than younger children.

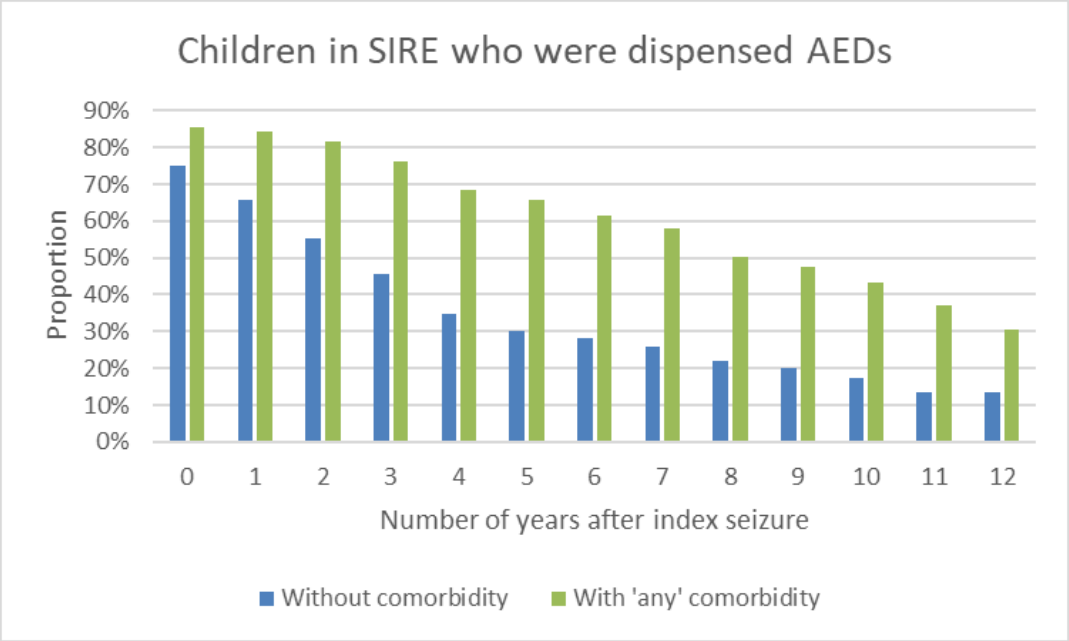

Figure 9. Proportion of children with unprovoked seizures with and without comorbidity receiving AEDs x years after the index seizure. N=769.

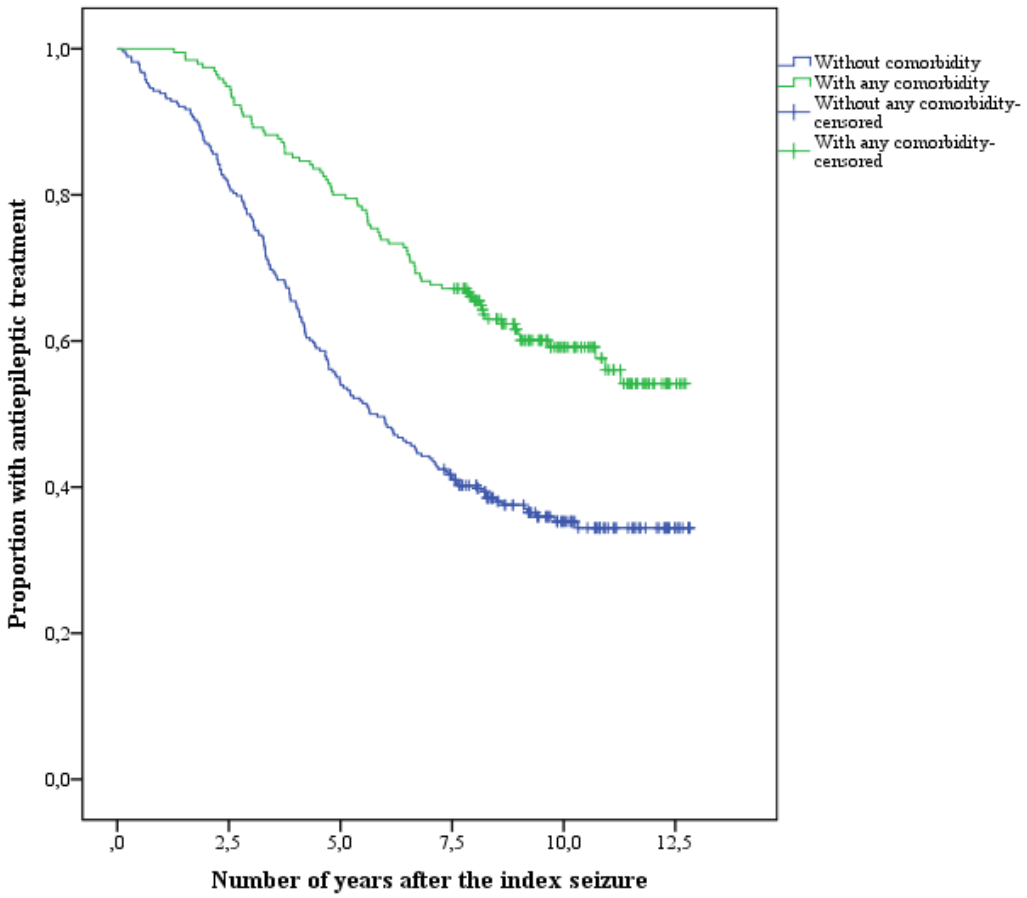

Figure 10. Survival function for discontinuing AED medication[1]. N=473.

[1]Analysis of all children SIRE (index dates between Sept 1st 2001 till Dec 31st 2006) who received AED any time after the index date and after the start of SPDR (July 1st 2005) up until Dec 31 2014. Adjusted for age and sex.

6.6 TREATMENT WITH ANTIDEPRESSANTS, NEUROLEPTICS AND DRUGS FOR ADHD IN CHILDREN WITH SEIZURES (*STUDY IV*)

Drugs for treatment of ADHD were dispensed to 31/769 (4%) of the children in SIRE four years after the index seizure, and to 38/769 (5%) after eight years. This was the case more often for those with recurrent seizures than those with a single seizure at baseline. Those with any comorbidity, and in particular ADHD, were treated in a much higher proportion compared to those without comorbidities. The OR to be treated with ADHD medication four years after index was 16.5 (95% CI: 6.9–39.5) and eight years after index 8.8 (95% CI: 3.7–20.8) for those with ADHD at baseline compared to those with no comorbidity (Table 3).

Antidepressant were dispensed to 13/769 (2%) four years after index and to 23/769 (3%) eight years after index. Lower age was associated with fewer antidepressants dispensed while a neurodevelopmental comorbidity or CP at baseline indicated towards an association with more children receiving antidepressants (OR after 8 years; 2.3 95% CI: 1.0–5.5) (Table 3).

Few children were treated with neuroleptics, only 10/769 (1%) at four years and 19/769 (2%) at eight years. Children with a neurodevelopmental comorbidity or CP at baseline were more likely to also receive this treatment compared to those without comorbidity (OR after 8 years: 6.9, 95% CI: 2.4–19.8), especially those with autism spectrum disorder (OR after 8 years: 9.1, 95% CI: 2.2–37.4) (Table 3).

		neuroleptics			
		4 years		8 years	
	Total N	N (%)	OR[1] (95% CI)	N (%)	OR[1] (95% CI)
Number of seizures at baseline[2]					
One seizure	255	3 (1)	ref	3 (1)	ref
Recurrent seizures	514	7 (1)	1.1 (0.3-4.4)	16 (3)	2.9 (0.8-10.3)
Comorbidity at baseline					
Without comorbidity	519	1 (0.2)	ref	5 (1)	ref
With any comorbidity	250	9 (4)	22.2 (2.8-178.2)	14 (3)	6.9 (2.4-19.8)
Intellectual disability	119	4 (3)	2.4 (0.5-11.2)	8 (7)	2.0 (0.5-7.3)
CP	68	1 (1)	1.3 (0.1-14.6)	1 (1)	0.5 (0.1-4.8)
Autism Spectrum Disorder	50	2 (4)	1.8 (0.3-11.5)	7 (14)	9.1 (2.2-37.4)
ADHD	49	3 (6)	6.3 (1.2-33.5)	1 (2)	0.4 (0.0-3.9)
		antidepressants			
		4 years		8 years	
	Total N	N (%)	OR[1] (95% CI)	N (%)	OR[1] (95% CI)
Number of seizures at baseline[2]					
One seizure	255	7 (3)	ref	11 (4)	ref
Recurrent seizures	514	6 (1)	0.3 (0.1-1.0)	12 (2)	0.5 (0.2-1.1)
Comorbidity at baseline					
Without comorbidity	519	6 (1)	ref	12 (2)	ref
With any comorbidity	250	7 (3)	2.8 (0.9-8.7)	11 (4)	2.3 (1.0-5.5)
Intellectual disability	119	2 (2)	0.5 (0.1-3.9)	3 (3)	0.5 (0.1-2.4)
CP	68	1 (1)	3.8 (0.3-53.5)	2 (3)	2.6 (0.5-14.3)
Autism Spectrum Disorder	50	1 (2)	1.2 (0.1-13.6)	2 (4)	1.8 (0.3-10.0)
ADHD	49	2 (4)	4.6 (0.7-30.0)	3 (6)	2.7 (0.7-1.4)
		ADHD medication			
		4 years		8 years	
	Total N	N (%)	OR[1] (95% CI)	N (%)	OR[1] (95% CI)
Number of seizures at baseline[2]					
One seizure	255	6 (2)	ref	9 (4)	ref
Recurrent seizures	514	25 (5)	2.4 (1.0-6.1)	29 (6)	1.9 (0.9-4.1)
Comorbidity at baseline					
Without comorbidity	519	4 (1)	ref	15 (3)	ref
With any comorbidity	250	27 (3)	18.0 (6.1-52.8)	23 (9)	3.6 (1.8-7.2)
Intellectual disability	119	6 (5)	0.7 (0.2-2.2)	4 (3)	0.5 (0.1-1.6)
CP	68	4 (6)	2.7 (0.8-9.7)	4 (6)	1.9 (0.6-6.2)
Autism Spectrum Disorder	50	4 (8)	1.2 (0.3-4.4)	1 (2)	0.2 (0.0-1.8)
ADHD	49	15 (31)	16.5 (6.9-39.5)	12 (24)	8.8 (3.7-20.8)

Table 3. Comorbidities and number of children treated with neuroleptics, antidepressants, or with drugs against ADHD 4, and 8 years following a first unprovoked seizure in children.

[1]Odds Ratios (ORs) adjusted for age groups and sex. [2]Information abstracted from medical records covering six months' post index seizure, and pertaining to pre-index seizure, index seizure, and any subsequent seizures within six months from the index seizure, and information on comorbidities.

7 DISCUSSION

With SIRE, a large population-based cohort of patients with newly diagnosed unprovoked seizures, was established. A crude incidence rate of a first unprovoked seizure of 67/100 000 person years was found in children, the highest rate being before the first birthday. One-third of these children were identified having neurodevelopmental comorbidity or CP and two-thirds had experienced recurrent seizures already at baseline. Two years later more than two-thirds of the children had been seizure-free for 12 months with or without AEDs, while only 50% of the children with neurodevelopmental comorbidity or CP at baseline achieved this. Eight years after the index seizure, children with comorbidity were dispensed AEDs four times as often as those without comorbidity. In addition, more neuroleptics and drugs for ADHD were dispensed to those with neurodevelopmental comorbidity or CP at baseline.

7.1 DISCUSSION ON MAIN FINDINGS

7.1.1 Incidence of seizures

SIRE was set up to enable a long-term follow-up of a rather large population in a resource-effective manner. This large number of patients with a first unprovoked seizure identified in an urban population gives possibilities for further studies using the public registries by the unique personal number of all individuals in Sweden. Additionally, at the time, the incidence of seizures had not been described in such a large population-based material.

The overall incidences of all ages found in SIRE was lower than the 51–74/100,000 reported in other studies from Europe and the US, and this was particularly true in the elderly population (Fiest et al., 2017; Forsgren et al., 2005; Olafsson et al., 2005). However, the overall incidence in children was within the range of previous studies, which indicates a good ascertainment of the paediatric cases in the area. A slightly higher age-specific incidence for those younger than one year was detected. The incidence found for the first year of life has shown a tendency to increase also in other more recent studies (Aaberg et al., 2017a; Camfield and Camfield, 2015; Larsson and Eeg-Olofsson, 2006; Saarinen et al., 2016). There were more patients in the whole SIRE cohort with unclassified seizures than observed by others (Aaberg et al., 2017a) presumably due to: the short follow-up time; medical records being the only source of information (with no standardised work-up); and strict application of criteria for classification. However, the distribution of sex, seizure type and identified aetiologies in the whole SIRE cohort was consistent with other studies (Christensen et al., 2007b; Gao et al., 2018; Jallon et al., 1999; Oun et al., 2003; Wang et al., 2019a; Zarrelli et al., 1999), which suggests that the methodology had no major selection bias when identifying the cases.

7.1.2 Neurodevelopmental comorbidities and CP in children with seizures

There have been concerns that seizures per se, or the antiepileptic treatment, might contribute to the increased prevalence of comorbidities in children with epilepsy. In contrast to epilepsy,

neurodevelopmental comorbidities and CP can usually not be given an exact starting date, which complicates the analysis.

Neurodevelopmental comorbidities and CP were found in 32 % of the children in SIRE, already at the baseline assessment. This is similar to a Norwegian study, observing developmental and/or psychiatric disorders in 42.9% of children with epilepsy, which they compared to findings of only 6.6% with these disorders in the general population (Aaberg et al., 2016). Surprisingly, at the 2-year follow-up of SIRE the number of children with comorbidities did not increase much, which indicates that many of the comorbidities are possible to identify and diagnose already at seizure debut. This supports the idea of a common cause resulting in both seizures and the comorbidity, rather than the idea of a causal relationship between the two. A comorbidity between epilepsy and mood disorders has been found to have a relative negative impact on the patients' quality of life and lead to an increased consumption of medical services (Cramer et al., 2003; Johnson et al., 2004; Kanner et al., 2010). A comorbidity has also been found to elevate the already increased risk of premature death in patients with epilepsy (Abdel-Mannan and Sutcliffe, 2019; Christensen et al., 2007a; Fazel et al., 2013).

7.1.2.1 Seizures and cerebral palsy

Cerebral palsy (CP) and seizures have traditionally been regarded as closely related, with 20–45% of children with CP developing epilepsy (Cooper et al., 2017; Gabis et al., 2015; Odding et al., 2006). A Swedish population study found the prevalence of CP in children born from 2007–2010 to be 1.96/1000 live births (Himmelmann and Uvebrant, 2018). A Norwegian registry study found the prevalence of CP to be 13.9% in children with epilepsy, giving an OR of 55.9 (95% CI: 50.4–62.0) compared to the general population (Aaberg et al., 2016). In *Study II and III* of this thesis the prevalence of CP was found to be 9%, which is elevated but still lower than other studies of children with seizures, which may be attributable to the fact that this cohort also includes children with only one seizure and not only those with a diagnosis of epilepsy.

7.1.2.2 Seizures and ADHD

ADHD has been found to be 2–7 times more common in children with seizures than in the general population, with a prevalence of 12–38% (Aaberg et al., 2016; Bertelsen et al., 2016; Brikell et al., 2018; Reilly et al., 2014). However, one study in children with epilepsy with good seizure control and without intellectual disability found a prevalence of ADHD of 6.9%, well comparable to the prevalence in the general population (Kim et al., 2012). Another study demonstrated that children with epilepsy had ADHD more often than the general population, and that the risk increased with early onset age of seizures, frequent seizures and treatment with multiple AEDs (Wang et al., 2019b). An association with specific epilepsy syndromes has also been seen, with symptoms of ADHD in Frontal Lobe Epilepsy, Childhood Absence Epilepsy and Childhood Epilepsy with Centrotemporal Spikes (Parisi et al., 2010). The low prevalence of ADHD found in *Study II and III* may partly be explained by incomplete

information in the medical records. Additionally, ADHD has been considered a diagnosis relevant primarily for school-aged children, and consequently part of the cohort was too young for a possible evaluation for an ADHD diagnosis.

7.1.2.3 Seizures and intellectual disability

Intellectual disability has been found to be 30 to 40 times more common in children with epilepsy compared to those without (Aaberg et al., 2016; Chiang and Cheng, 2014). The prevalence of intellectual disability in children with epilepsy has been reported to be as high as 40% (Oh et al., 2017; Reilly et al., 2014; Sillanpaa, 1992). The prevalence of 16% in *Study II and III* was thus lower than expected, but still elevated compared to a presumed prevalence of about 1% in the general population (Maulik et al., 2011; Westerinen et al., 2014). The explanation for the low number again probably being that there was no standard work-up in SIRE and the inclusion of young children. Only rarely is a diagnosis of intellectual disability confirmed before three years of age. The elevated rates of intellectual disability in children with epilepsy could possibly partly be attributed to the seizures in specific epilepsy syndromes like the 'Epileptic Encephalopathy With Continuous Spike and Wave During Sleep' (CSWS) syndrome and Landau-Kleffner syndrome (Besag et al., 2016b), but given the prevalence is already high at seizure debut in many studies the theory of a common cause to both seizures and intellectual disability seems more likely in the majority of cases.

7.1.2.4 Seizures and autism spectrum disorder

A clear association has been shown between autism spectrum disorders and epilepsy with the one disorder coexisting in up to 20% in the other, but the cause of this association is still to a large extent unknown and debated (Besag et al., 2016; Lukmanji et al., 2019; Strasser et al., 2018). Autism spectrum disorder is more common among boys in the general population (3:1) and this is also the case in children with seizures and ASD. However, in a study of different types and groups of ASD, the strongest association with epilepsy was found among females with an intellectual disability (Jokiranta et al., 2014; Loomes et al., 2017). Autism has been found in about 5% of the children with newly diagnosed epilepsy, and in almost 15% of the children with a new diagnosis of epilepsy and intellectual disability (Berg et al., 2011b). In the present studies ASD was found in 6.7% of the children. Out of these 50 patients, 34, or 68% were also found to have an intellectual disability. A point prevalence of 6.2/1000 of ASD was reported in the general population in a study of pre-schoolers from almost the same catchment area as these studies (Fernell and Gillberg, 2010).

There is an ongoing discussion regarding whether epilepsy in some cases can result in symptoms of ASD (Besag et al., 2016). Arguments are made that some children with ASD lose skills early in life and this might be caused by (subclinical) seizures. This has been hypothesized since studies have found epileptiform discharges in more than half of children with ASD without other symptoms of epilepsy, and treatment with AEDs sometimes normalised the EEG (Chez et al., 2006). However, no evidence has been found that this normalisation have any therapeutic effect on the core symptoms of ASD (Tharp, 2004).

Others suggest a common molecular pathway between epilepsy, ASD and intellectual disability since genetic defects as well as similar types of brain pathology have been found in the different disorders (Tuchman and Cuccaro, 2011). The high prevalence of autism (and intellectual disability) already at the onset of seizures in *Study II and III* suggest a common cause to the disorder rather than a causal relationship.

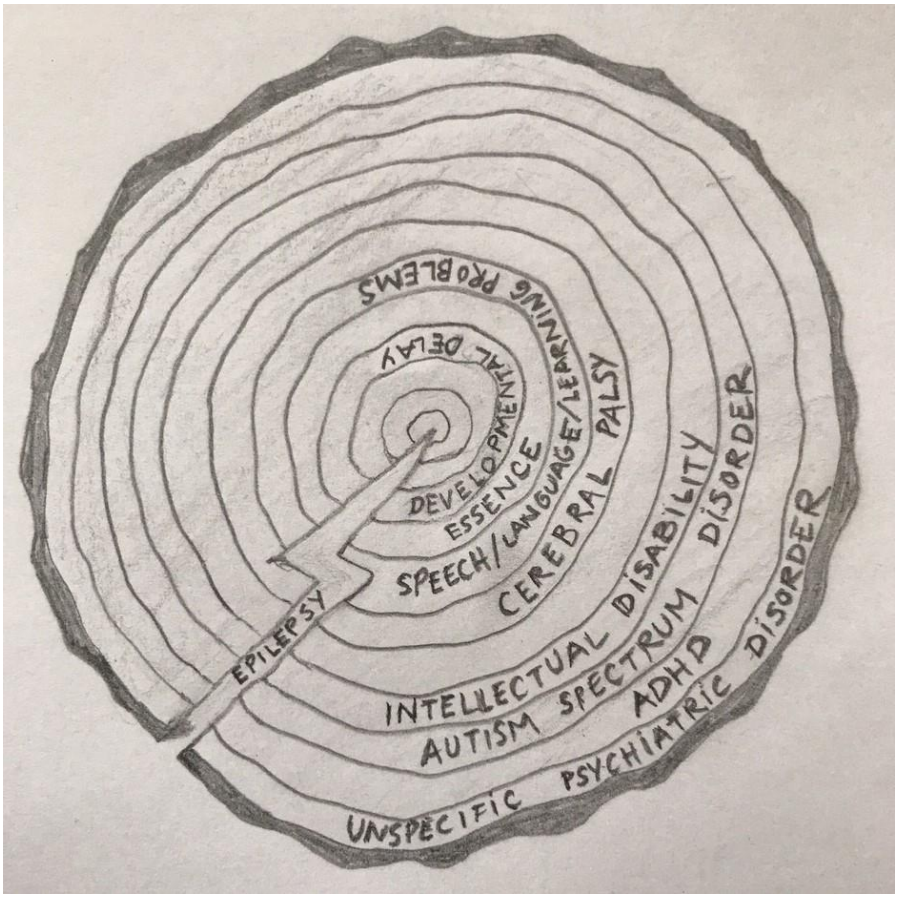

Figure 11. Growth rings on a tree, by Eva Åndell Jason. Epilepsy is diagnosed in all ages, while some of the discussed comorbidities are more age-specific.

7.1.2.5 Seizures and psychiatric diagnosis

Depression and anxiety are other diseases found in a higher prevalence in children with epilepsy, than in the general population. Some studies have demonstrated a correlation between depression/anxiety and different seizure variables such as seizure control, age of seizure onset, polypharmacy with AEDs and the type of epilepsy, while others do not (Alfstad et al., 2016; Cianchetti et al., 2018; Davies et al., 2003; Kwong et al., 2016; Schraegle and Titus, 2017). Anxiety and depression are generally more common in girls, but the differences between boys and girls have been found to be smaller in adolescents with epilepsy (Jones et al., 2015; Reilly et al., 2014). Population-based studies in Sweden,

Denmark and Finland have also shown higher rates of psychosis in adults with epilepsy than in the general population (Adelow et al., 2012; Clarke et al., 2012; Qin et al., 2005).

The 2.5% (19/766) paediatric patients identified with a psychiatric comorbidity in *Study II* is probably a sign of underassessment due to the assessment through medical records with limited information, and to the fact that there was no access to the records from child psychiatry at this time point. Over 70% of the children were also younger than 10 years old at the time of assessment, and most of the included diagnoses are very rarely diagnosed before that age.

7.1.2.6 Seizures and ESSENCE

A large group of children, 34% (107/315), with seizures and who were younger than six years old, had unspecific cognitive, developmental and learning disabilities grouped under the acronym ESSENCE (Gillberg et al., 2014). The concept of ESSENCE implies that children with ESSENCE probably will receive a more specific diagnosis later in life, but have more unspecific neuropsychiatric cognitive symptoms before they are six years of age. The prevalence of ESSENCE in the general population is estimated to be 5–7% (Gillberg, 2010). Contrary to other reports of ESSENCE, boys were not overrepresented in our material, in spite of boys having more seizures per se (Aaberg et al., 2017a; Gillberg, 2010). Unspecific problems in younger children were well described and documented in the medical records which facilitated identification with the ESSENCE method.

7.1.2.7 Seizures and multiple comorbidities

As discussed earlier, more than one comorbidity is commonly observed. This was found at baseline in 87/766 (11.4%) in *Study II*. A very large study analysing six million children regarding 12 neurobehavioral comorbidities found multiple comorbidities in 36% of children with newly diagnosed epilepsy compared to in only 8% of those without epilepsy (Oh et al., 2017).

Children with epilepsy and cognitive difficulties have been found to have stronger associations with depression, anxiety and autism than children with epilepsy ‘only’ (Aaberg et al., 2016; Buelow et al., 2003; Caplan et al., 2005). Children with epilepsy and psychosis have also been found to more often have other comorbid neurodevelopmental diagnoses (like autism and intellectual disability) than children with psychosis only (Lax Pericall and Taylor, 2010). As mentioned earlier in this discussion, these results support the hypothesis of a common cause to the different disorders.

7.1.3 Seizures - prognosis and treatment

7.1.3.1 Seizure prognosis – short term

In *Study III* seizure freedom during month 13–24 after the index seizure, or the start of treatment with AEDs, was studied. Of the 750 patients, 69% were seizure-free in year 2, with or without treatment. A negative impact on seizure freedom was seen in those with

neurodevelopmental comorbidities and CP at index, and for those who had had already more than one seizure at the baseline assessment. This confirms earlier findings regarding comorbidities and recurrent seizures close in time to seizure debut (Brorson et al., 2019; MacDonald et al., 2000; Tsubouchi et al., 2019), likely reflecting that epilepsy often is one of a variety of symptoms in children with neurological disturbances, and that comorbidities imply a more severe disturbance of the brain function. This agreeing with the concept that children with multiple diagnoses have a more complex phenotype of an underlying cause (Tuchman and Cuccaro, 2011).

7.1.3.2 Treatment with AEDs – long term

According to the current definition epilepsy is first resolved after 10 years without seizures, and at least five years without treatment (Fisher et al., 2014). Less than 50% of all the children in SIRE were dispensed AEDs four years after index, and one-third after eight years. However, after eight years, half of those with any comorbidity were still dispensed AEDs. Between Sept 1st 2005 and Dec 31st 2014, there was a 40% lower chance that those with any comorbidity discontinued medication, compared to those without comorbidity. Assuming that most of these children stopped using AEDs due to seizure freedom indicates a rather good overall long-term seizure prognosis in children. Similar results have indeed been reported by others (Moosa, 2019). Furthermore, from the perspective of this endpoint a negative influence of neurodevelopmental comorbidity and CP and repeated seizures at baseline could be seen. This confirming other studies where seizure frequency, aetiology and IQ during the first years of the seizure disease influenced the future remission of childhood epilepsy (MacDonald et al., 2000; Sillanpaa et al., 2014; Tsubouchi et al., 2019). This once again stresses the importance of evaluating children with seizures for neurodevelopmental comorbidities and CP.

7.1.3.3 Treatment with antidepressants, neuroleptics and drugs for ADHD in children with seizures

After studying the prevalence of different comorbidities in children with seizures, an evaluation of pharmacological drug treatment of some of these disorders was performed. *Study IV* found that surprisingly few children from SIRE were treated with neuroleptics (1–2%), antidepressants (2–3%) or drugs for ADHD (4–5%). However, they were still dispensed 2-10 times more frequently in this group of children with seizures, than what was reported from the official health statistics of all children 0–19-year-olds in the county of Stockholm, Sweden. Neuroleptics were dispensed to 1.4/1000 of 0-19 year-olds in the general population of Stockholm in 2006 (the first year with complete data in SPDR) and to 2.34/1000 of them in 2014 (the last year of follow-up of the SIRE cohort). At the same time points, antidepressants were dispensed to 4.6/1000 (2006) and to 9.9/1000 (2014), and drugs for ADHD to 4.3/1000 (2006) and to 22.2/1000 (2014) of the children in the general population.

When an individual suffers from two different disorders, one of the diseases may gain precedence over the other, leading to the underassessment and no treatment of the other.

Many things may influence the use of medical treatment of the seizures, as well as the comorbidities. Drugs for comorbidities might lower the threshold for seizures, there can be interactions between the drug for the comorbidity and AEDs, and symptoms of depression and anxiety have been seen as adverse effects of many AEDs (Kanner and Dunn, 2004; Mula and Sander, 2007). When more than 100 children with epilepsy were evaluated for psychiatric disorders, 2/3 had a psychiatric diagnosis, but only 1/3 received any mental service (Ott et al., 2003). Many guidelines, including those from the Swedish Medical Products Agency (MPA) (Läkemedelsverket, 2016), recommends caution with treating ADHD with methylphenidate in children with seizures. This is in spite of consistent findings and conclusions that there is no evidence that drug treatment of ADHD in children with epilepsy causes seizures (Besag et al., 2016a; Brikell et al., 2019; Gucuyener et al., 2003; Hamoda et al., 2009; Parisi et al., 2010) . Treatment of depression with selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitors (SNRI) has instead shown to potentially decrease the risk of seizures (seizures were in this study not defined as epileptic, but as not provoked by an identifiable factor like alcohol withdrawal, and with a possible relationship to the drug studied) (Alper et al., 2007). Some neuroleptics used for treatment of psychotic symptoms in children with epilepsy may decrease the seizure threshold (Hedges et al., 2003; Jerrell and McIntyre, 2008; Kumra et al., 1996; Remschmidt et al., 2000), but risperidone used to treat behavioural disorders in 54 children with epilepsy gave no changes in seizure frequency (Holzhausen et al., 2007).

7.2 DISCUSSION ON METHODOLOGY

The scientific value of a study is based on its internal and external validity. To be reliable and of interest to others, the study should have measured what it was supposed to measure (internal validity) and the results should be generalizable to other populations than the one studied (external validity).

Large, well performed randomised controlled trials (RCTs) provide the strongest evidence for causal associations and are crucial for the formulation of clinical recommendations. However, non-randomised observational studies, like cohort studies and case-control studies, can sometimes be the only possible or optimal design (Rothman, 2012). This is, for example, the case when the outcome is rare or when ethical issues prevents RCTs.

7.2.1 Random error

Errors exists in all studies; they can be random and give the results a low precision. Precision is affected by the size of the study population and the choice of study design. The precision of a statistic estimated within in a study can be described by the confidence interval. The interpretation of a 95% confidence interval is that if we used the same method with a different sample from the same underlying population, and compute an interval estimate for each sample, we would expect the true population parameter to fall within the interval estimates 95% of the times (Rothman, 2012).

The fact that this thesis is based on a relatively large registry gives the studies fairly good precision regarding incidence of seizures. Still, within subgroups of specific comorbidities, and for estimation of associations with specific treatments including AEDs, neuroleptics, antidepressants and drugs for ADHD the numbers were sometimes small which is reflected by wide confidence limits around the OR and HR estimates, making the results uncertain. Furthermore, due to small numbers, we could not analyse specific epilepsy syndromes separately.

7.2.2 Systematic errors

Errors can also be systematic and lead away from the correct answer. Systematic errors are also called 'bias' and includes selection bias, misclassification and confounding.

7.2.2.1 Selection bias

Selection bias is when the studied population differs from the source population and can be due to patients with problems being more willing to answer a questionnaire, a drug treatment leading to more medical visits and then giving a higher frequency of detected problems or admission rate bias where individuals with many diagnoses are more often found in patients at a hospital (Rothman 2012). Such selection bias may influence generalisability of the results to the underlying population and also distort associations between investigated exposures and outcome.

For all of SIRE there was a likely underassessment of seizure patients among the elderly, due to a larger number of potential caregivers in the area. The assessment at the hospital departments was done by the research nurse, but there are difficulties in keeping a large network with many caregivers reminded of the task to submit cases and some might have been unwilling to report cases due to lack of time. However, the risk of underassessment of children seems substantially smaller. The standard practice in the area was to refer children with seizures to the neuropediatric department at Karolinska University Hospital, even though a few patients might have been referred to other hospitals or stayed at an outpatient clinic outside the hospital. With regard to adults, and particularly the elderly, there were more alternatives for seizure care. Also some patients had their index seizure in other cities, when travelling, but most of them were identified by SIRE when referred for follow-up to their 'home hospital' in Stockholm. Nonetheless, the cases had a similar composition regarding sex, seizure type and aetiology as seen in other studies (Christensen et al., 2007b; Gao et al., 2018; Jallon et al., 1999; Oun et al., 2003; Wang et al., 2019a; Zarrelli et al., 1999), which suggests that selection bias was minor in SIRE. The potential underassessment will lead to underestimated incidence particularly in *Study I* (all ages), but may also be an issue in *Study II* (children).

The prevalence of comorbidities might be over-estimated, since children with more than one medical problem may be examined by medical professionals more often, and questions regarding symptoms of seizures might be discussed and incident seizures be identified and more children with comorbidities might be included in SIRE in this way. Compared to the

general population children with seizures have more frequent medical visits, why neurodevelopmental comorbidities and CP might be recognized more often. This may to some extent contribute to the large differences in the prevalence of such comorbidities observed between the children included in SIRE and the general population (*Study II*).

Loss to follow-up can introduce selection bias if those remaining in the study had a different level of exposure e.g. prevalence of comorbidities/ or outcome, e.g. prognosis, then those not staying in the study. Importantly, there was virtually no loss to follow-up in the 2-year follow-up, minimizing potential selection bias (*Study III*). Moreover, a particular advantage of using registry data for follow-up (*Study IV*), is it can be expected to be complete for all participants. This is true for the Swedish Prescribed Drug Register which covers all dispensed medications in Sweden.

7.2.2.2 Misclassification bias

Misclassification bias is introduced when the measurements are incorrect, so that some persons who have a disease of interest (or exposure) are classified as not having the disease or vice versa.

Misclassification of seizures;

All data were assessed in a standardised way, according to the predefined research protocol (which was based on the prevailing ILAE recommendations (1981, 1993)) and all medical charts were read by at least two members of the research group in order to strengthen the internal validity. To have a first seizure, and not a diagnosis of epilepsy, as the inclusion criteria strengthens the internal validity, since the diagnosis may be delayed in the clinic and the definition of epilepsy has changed over time. A first diagnosis of epilepsy as inclusion criteria might include children who have been having seizures for quite some time, which could tamper the outcome. However, not everyone seeks medical assistance already at the first seizure (might be a short event not really attended to, until more have happened). In SIRE as many as 25% were assessed to have had, at least one, probable, unattended, unprovoked seizure already before the index seizure (the first one for which the patient sought medical assistance). The seizure diagnosis, of the index event, was decided on, and re-evaluated, by the research team so as to consistently validate the diagnoses.

Being dependent on medical records as the source for information, but with no influence over the quality of the records or what procedures had been followed, such as EEG, is a limitation. As an example, the low rate of performed neuroimaging could affect the reliability of the seizure types and the aetiological classifications, but the presumed aetiologies found, agreed with findings from other studies (Aaberg et al., 2017b; Gao et al., 2018; Hirfanoglu et al., 2017; Olafsson et al., 2005; Wang et al., 2019a). Medical records as the data source might lead to some non-differential misclassification towards ‘unknown’, especially since the research team used classifications of seizure type strictly. The relatively short follow-up time of six months used for baseline information probably also led to some misclassification, since it is not always possible to make seizure classifications in that time. Misclassification

regarding seizure types and aetiology could be both differential and non-differential in these studies; EEG and brain imaging were possibly performed more often in children with a comorbidity, and could then overestimate the specific classifications in that group.

Misclassification of comorbidities;

With regard to comorbidities, no formal assessment was made of the patients with suspected comorbidities, which gives an uncertainty for some of the diagnoses. Instead this information was based on a clear problem description in the medical records. This was a choice made to avoid a substantial underassessment due to the long waiting times for neuropsychological evaluation at the time. Access to records from child psychiatry was restricted, which meant that knowledge of a clinic assessment was dependent on information from the parents to their career. At the 2-year follow-up comorbidities were found in 8% of children not diagnosed with comorbidity at baseline, and in 2% (n=16) of the children the diagnosis of comorbidity was no longer valid, showing good consistency (12/16 children belonged to the ESSENCE group).

Assessment of neurodevelopmental comorbidities and CP at baseline were based on data at the time of seizure onset and the following six months. Based on this we find it unlikely that they were caused by longstanding exposure to a seizure disorder or treatment with AEDs. It should however be mentioned that 25% of the children had experienced seizures before the one for which they sought medical assistance (the index seizure).

When reading medical journals, information might be interpreted in different ways by different individuals (interviewer bias). To reduce this potential bias, more than one person assessed all medical journals.

Misclassification of recurrent seizures;

The information on the outcome seizure remission was also collected from the medical journals. Most patients had regular contact with their treating physician, either by visits or phone calls. Not all may be able to report the seizure frequency in a reliable way. This is probably more of a problem when the child had more frequent seizures, and the parents had difficulties remembering them all. On the other hand, parents to children with few seizures might also forget more frequent seizures more distant in time if reporting to the caregiver infrequently. Children with comorbidities might have had a more frequent contact with their treating physician, and then remembered to report more seizures, which might have made the association between co-morbidity and recurrent seizures during the 24 month follow-up stronger (*Study III*).

Misclassification of drug treatment;

Information of drug use in *Study III* was also assessed from the medical journals. This was drugs prescribed, which is known to be an over-assessment of drugs used since all drugs may not be collected by the patient. Children with comorbidities might have been treated with

other drugs as well, and poly-pharmacy increases the risk of non-compliance (Erickson and Yang, 2019; Ofori-Asenso et al., 2018) why drug use might have been overestimated in this group. Non-compliance might have made the association between the comorbidities and lack of seizure remission in *Study III* stronger. A strength in *Study IV* is that we can confirm the association between comorbidities and drug use with the Swedish Prescribed Drug Registry (SPDR). The data collection for SPDR is done by a state owned company responsible for the pharmaceutical services in Sweden, with the data collected from the prescription software, which reduces this risk. SPDR does not give information on drugs prescribed, but on drugs dispensed in other to reduce the effect of lack of compliance (Wallerstedt et al., 2016; Wettermark et al., 2007) (*Study IV*).

In *Study IV* we also used information from the SPDR to retrieve information on neuroleptics, antidepressants and drugs for ADHD. The SPDR is available from July 2005, which is a limitation since the index seizures were collected already from September 2001. To have the same data on all the children, and to not include an unknown confounder, we chose to study drugs dispensed four and eight years after index.

The fear of neuroleptics, antidepressant and drugs for ADHD, lowering the threshold for seizures might have decreased the number of drugs dispensed among these children with known seizures, compared to the general population.

As mentioned earlier this group of children with seizures visit a neuropeadiatrician more often than the general population, and it is known that more frequent hospital visits lead to more drug prescriptions. This affects the comparison between drug treatment in children of SIRE and that of the general population of children. Within SIRE, the association between comorbidities and drugs dispensed might be overestimated for the same reason (*Study IV*).

7.2.2.3 Confounding

Confounding is a factor associated with both the exposure and outcome that is being studied. Failure to adjust for such a factor may result in spurious associations between exposure and outcome. E.g. being the youngest in the family is not the cause of Mb Down, it is a confounder in the association between maternal age at delivery and the risk of Mb Down in the child.

Age and sex are often confounders, both seizures and most of the comorbidities studied are more common in boys. Incidences and ORs and HRs were calculated adjusted for age and sex. When analysing the individual comorbidities, they were mutually adjusted, since they often covariates with one child having more than one comorbidity (*Study III*). When analysing the HR for discontinuation of drugs we adjusted additionally for single/recurrent seizures, comorbidity yes/no and date of index. Date of index was valuable since some children had their date of index years before SPDR was up and running, while others were included when SPDR was available.

Socioeconomic factors could also be a confounding factor, since some of the comorbidities are overrepresented in families with a lower income and education. Adherence to treatment with AEDs may be lower in children in families with low education, and this could result in a higher risk of recurrent seizures. It is also known that use of prescription drugs is higher in these groups (Weitoft et al., 2008). This may contribute to an association between comorbidity and future treatment with e.g. ADHD medication. It is noteworthy that there was no association between the risk of unprovoked seizures and socioeconomic status (SES) or education in previous studies based on SIRE (Adelow et al., 2011, 2012; Mahler et al., 2018). Unfortunately access to information regarding SES and parents' education was incomplete in the younger age groups, why we could not adjust for SES.

7.2.3 Generalizability

Since these are large population-based studies with minimal loss to follow-up the external validity should be good and findings should be generalizable to other settings with a similar aetiological pattern for seizures, and similar treatment strategies as in Stockholm, Sweden.

Health care is easy accessed in Stockholm, Sweden, and free of charge for children. Prescribed drugs were also heavily subsidized by the government (but not free of charge) during the study period. This might affect the generalizability regarding treatment, to other settings where the health care system differs. However, it should make the data regarding seizure incidence and prevalence of comorbidity more reliable since medical visits are less dependent on the family income.

Treatment strategies regarding ADHD have shown great differences in different parts of Sweden, and also over time there has been a larger increase of children in Stockholm being treated compared to other counties (Socialstyrelsen). In the general population of Stockholm, the children were dispensed drugs for ADHD 5 times more often in 2014, than in 2005. This complicates the comparison with other settings and over time, but it should not affect the association between neurodevelopmental comorbidities and drugs dispensed.

The association between neurodevelopmental comorbidities and CP and poor seizure prognosis should in large be generalizable to other settings.

7.3 CONCLUSIONS

- The incidence of unprovoked seizures in Stockholm is similar to that in other high-income countries. The crude incidence rate of all ages was 35.4/100, 000 person years, with the highest incidences found among the youngest and the elderly. In children 0–19 years old the incidence rate of seizures was 67/100,000, highest during the first year of life (204/100,000).
- The index-seizure was most often classified as focal (62% in all ages, and 50% in children). There was a comparably high amount of seizures that remained unclassified, probably due to short follow-up, dependence on medical records and strict application of classification criterias. However, the pressumed aetiologies found

were similar to other studies, with stroke (11%) and brain tumours (9%) being the most common causes. Neurological deficits from births was found in 10% of the patients. Many of these deficits are risk factors for the comorbidities studied.

- A higher prevalence of neurodevelopmental comorbidities and CP was found in children with a first unprovoked seizure compared to what is seen in the general population. This supports the hypothesis that innate neurological disturbances are responsible for both the seizures and the other neurodevelopmental symptoms.
- Neurodevelopmental comorbidities and CP at baseline had a negative association with seizure remission within two years, regardless of treatment with AEDs or not.
- Children with neurodevelopmental comorbidities and CP at baseline were dispensed AEDs, neuroleptics and drugs for ADHD more often than what was dispensed in the general population, four and eight years after index.

This supports the hypothesis that innate neurological disturbances are responsible for both the seizures and the other neurodevelopmental symptoms, and that neurodevelopmental comorbidities and CP have a negative effect on the prognosis of seizures in children.

7.4 CLINICAL IMPLICATIONS

With regard to neurodevelopmental comorbidities and CP it would contribute to the care of the patients if the neuropeadiatrician carefully screened for these types of diagnoses at the seizure debut. This is particularly so, since the comorbidities have a negative impact on the seizure prognosis, but also because the comorbidities addressed in this thesis merit specific management. The presence of comorbidities should also affect choices regarding treatment of the epilepsy, since more children in this group will be pharmacoresistant and also because more of them will use other drugs later on, increasing the risk of future potential drug interactions.

The thesis stresses the magnitude of the burden of epilepsy, since in many cases it also includes the burden of one or more comorbidities. Both patients with seizures, and patients with neurodevelopmental comorbidities and CP, have elevated risks of morbidity and mortality, which is why adequate resources should be allocated for identification and management of the disorders. This is a large and vulnerable group of children who would benefit from interdisciplinary team assessments (Nickels et al., 2016).

7.5 FUTURE PERSPECTIVES

SIRE can be used for further long-term studies regarding seizures. Case-control studies regarding the use of other drugs such as analgesics, antibiotics and melatonin could shed more light on the burden of disease on patients with seizures. Combining SIRE with other health care registries in Sweden can provide information regarding health-care and social issues. With the children becoming adults, outcomes such as education, child-bearing, and causes of death can be studied. SIRE has previously been used with different diagnoses from the Hospital Discharge Registry as exposure and with accident and injuries as both the

exposure and as the outcome. Being as large as it is, the SIRE cohort can to some extent be divided into different subgroups regarding seizure types, aetiology and early comorbidities.

Epidemiological studies like these give a helicopter perspective on the diseases studied. It would be of much interest to zoom in on the patients and validate the findings in a clinical context with, for example, an interview study of children with incident seizures in the area over a couple of years regarding neurodevelopmental comorbidities and CP. These children could later be included in a follow-up survey on seizure frequency and AED treatment. This would, of course, need new ethical approvals.

From a wider perspective, the findings of this thesis are consistent with others suggesting an innate cause/s to a neurodevelopmental complex. A continued search for these possible causes with imaging studies, genetic studies, immunological studies, etc. could give new leads for future treatments of uncontrolled seizures as well as the symptoms of neurodevelopmental comorbidities and CP.

8 ACKNOWLEDGEMENTS

TACK,

Kristina Tedroff – tack för att du adopterade mig som doktorand! Tack för struktur och pushning mot disputation. Tack för omtanke och mat vid nödsituation. Tack för Grundsund! Tack för stöd! Tack för skratt! Tack för sanity!

Per Åmark – tack för att du öppet tog med mig på denna resa trots mitt skeptiska forsknings-jag. Tack för allt tålamod och acceptans och tack för alla härliga mailkonversationer. De får mig att skratta, även när jag känner mig eländig – skriv en bok, asså en annan sort än den du redan skrivit!

Torbjörn Tomson – tack för alla knivskarpa formuleringar och tydliga aims. Tack för semesterarbete och för att du delar med dig av din kunskap och ditt kontaktnät.

Sofia Carlsson – tack för tålamod och stöttning! Tack för tydlighet och struktur, och alla tabeller. Tack för rim och reson. Och för att du är så kunnig och pedagogisk!

(**Anders Ahlbom** – tack för att du var med och startade upp SIRE, och för att du förde Sofia min väg).

Cecilia Adelöw – Nu förstår jag en del av allt du förstod när vi började forska ihop, att du stod ut med mig?! Du är en härligt mångfacetterad vän: konferenskompis, bokklubbskompis, mammakompis, nätverkskompis, långa viktiga samtalskompis mm. Och bästa, bästa forskningskompisen!

Eva Hellebro – att du orkade hålla ordning på alla papper och siffror vi (jag) strödde runt omkring oss (mig). Tack.

Statistiker Nicklas Pihlström – för att du räknar och förstår sådant som jag inte förstår. För att du raskt klev in på semestern och fixade siffror som saknades.

Statistiker Tomas Andersson – för att du lyckades förklara statistik för en nyförlöst, ammande mamma över telefonen, och för att du stöttat i bakgrunden långt efter att du behövde.

Anna Sandberg, KBH – för alla påminnelser om viktiga registreringar och för all hjälp inför disputationsansökan.

Pernilla Larsson, FoU Sörmland – för alla tidiga eftermiddagstider för mina presentationer och för snabba svar på mina mail.

None-Marie Kemp, KBH – för allt du hjälp mig med via mail, trots att du länge inte ens hade ett ansikte bakom dem.

Charlotte Palmstjärna – tack för att du tog dig an att bli mentor åt en helt okänd person. Tack Lisa för att du förmedlade kontakten.

Forskarskolan – för den energi jag fick av att gå på seminarier tillsammans med en massa smarta människor, och lära mig saker av personer som brinner för det de gör! För raster med kaffe o smörgås, och samtal med en massa underbart roliga o stöttande personer. Framför allt för **Anna, Karolina, Lisa och Martina** – för alla samtal, och gemensamt pluggande, för de graviditeter vi råkade samordna, och för att ni visat mig hur man gör detta med disputation. Du fick rätt Anna, det hände till sist i alla fall!

Institutionen för Kvinnors och Barns Hälsa och KI – trots att jag redan har gett mitt hjärta till Lunds universitet så har jag fått genomgå denna gedigna utbildning via Kvinnors och Barns Hälsa på Karolinska Institutet. Tacksamhet. Tack även för finansiellt stöd genom KID-medel.

FoU Sörmland – tack för generöst finansiellt stöd, stöd av bibliotekarie och statistiker, och engagemang och uppmuntran kring forskning i stort.

Tack även för generöst finansiellt stöd från **Margarethahemmet** och **UCB Nordic**.

Alla barn och familjer jag får träffa – ni lär mig så mycket om livet och tacksamhet. Känner mig ödmjuk inför allt ni delar med er av.

Arbetskamraterna både på Barn- och Ungdomskliniken och Habiliteringen i Nyköping – för att ni aldrig klagat (till mig) om min forskningstid, men framförallt, för allt ni kan och fixar! För att det är roligt att arbeta tillsammans med er, och all er kunskap! Och för alla roliga fester.

Helena, Wafa, Fredrik, Magnus (jag låtsas som att ni inte har slutat), **Faruk, Amerah** – Nyköpings barn, det här är era riktiga superhjältar. Jag är stolt över oss, och allt vi fixar!

Ulrika o Elin – som gör mina arbetsdagar roliga och rimliga! Som ser till att ”mina” patienter blir omhändertagna, även när jag inte är där. **Mats** – tänk att få ha dig som vikarie, vilken lyx.

Björn – för att du introducerade mig i barnneurologin, och för Per, så att detta projekt startades upp. För att du alltid visat intresse för hela mig, och alltid stöttat.

Barn – och Ungdomskliniken Sörmland - med **Diana** som alltid varit positiv till min forskning, **Charlotte**, som visat att det går och **Dan** som kommer efter, men ändå ligger långt före. Med **Susanne, Ann-Sofie, Hilla, Rosie och Carina** (de två sistnämnda iofs Hab) som löser allt sådant som jag inte fixar, och alltid frågar hur jag mår. Å **alla** ni andra!

ALB – kollegorna - Tack för alla skratt när jag jobbade med er. Och jag är så tacksam för att ni inte är längre än ett telefonsamtal bort, när det blir för klurigt.

Uppsala-barnneurologerna och övriga i regionen – ni känns närmre och närmre. Ansiktena bakom remiss-svaren skiner igenom och det gör mig glad (och arbetet roligare).

Lundafamiljen - ni är så många och det börjar bli alltför länge sen. Men; skål för glada minnen, skål för varje vår! Tack gymnasiegänget för minnen från nästan hela livet och tack studentlivsvännerna för den härligaste av tider! Jag tror att vår nästa vår närmar sig.

Nypangänget – past, present and future. Resorna, skidresorna, onsdagarna, kräftskivor, surströmming, matlagningsgänget, tjejträffarna som blivit tantträffar (som blev tonårsfest), fester, jourer, paddlingar, hamnen, sommarstugor, terapisnack, snack isf gym, ridläger, tårar och skratt, och nu även en disputationskompis. Vad mer kan man begära?

Övriga vänner – tänk vad mycket vi har hunnit med, trots att vi är så unga! Någon har jag känt hela livet, andra har jag sett världen tillsammans med och några ser jag barnen växa upp tillsammans med. Det som gäller er alla är att vi inte behöver ses ofta för att finnas för varandra! Jag vet att ni finns där. Det är stort.

Mamma – för all stöttning och för att du alltid tror på mig! För allt du lyssnat på. För all tid du lagt ner, allt från multiplikations-memory till skjuts, från barnvakt till fester. Jag minns när vi åt kinamat sittandes på köksgolvet i Västerås. *"Du och jag, Alfred! Du och jag, Emil!"(Astrid Lindgren).*

Pappa – för att du planterade drömmarna om studier och disputation, men med fokus på festerna och glädjen. Som alltid tror att allt går och vill att alla ska få göra roliga saker. Som alltid lyssnat när jag sagt till dig att göra det. Som inspirerar mina barn till att vara glada och se positivt på framtiden!

Patrik – för att du alltid har kunnat förklara så att jag förstår, och som alltid förstår (även litteratur på forskningsnivå, långt utanför ditt eget område). Tack för smörgåsarna med isbergssallad o majonnäs. Och för att du såg till att jag slapp göra pianoläxan. Vad mer kan man begära av en storebror?

Lena – för att du har gått före och banat vägen, för att du älskar mina barn, för många skratt och roligheter. För att du hjälpt mig med hemligheter. Och för att du hittade min man! Bättre syster går inte att få!

Lukas – för att du höll mig i örat som liten, och för att du är den finaste av storkusiner. För att du är klok och gör det du vill. För att du ser och förstår att uppskattar generationer. Lukas for president!

Linus – för att du gav mig förtroendet att hjälpa dig med postern på högstadiet, även om det visade sig vara ett misstag. För ditt och Emelies speciella band när ni var små, för alla skratt (tänker just nu på framträdandet med ”Avundsjuk” på midsommarafton) och för att du gör ditt eget i alla lägen!

Mia – för att du orkar med dina svenska kusiner, även efter en lång dag i skidbacken. Jag är så glad att du nått ditt första stora mål, det verkade bra mycket tuffare att nå, än att skriva den här boken! På tal om bok, ser fram emot att läsa en av dig framöver, i vilket genre det än må bli.

Mormor/far – er saknar jag! Det kommer över mig ibland. Hur glada ni hade varit för min skull. Hur varmt det hade varit med en kram. **Farmor/far** – er minns jag inte så mycket. Men jag vet att ni format mig genom det ni gett pappa. Önskar jag hade fått mer tid med er! **Alla generationer före dess** – jag funderar på er ibland. Vilka ni var? Vad ni skickat vidare till mig? Varför är vi plötsligt massor av läkare, sjuksköterskor o sjukgymnaster i en generation när nästan ingen i generationerna före jobbat inom vården? Vem var det som sådde fröet, som fick växa genom generationerna?

My american family – thank You for not only giving me a home for a year, but a family for a lifetime! My first medical research project was the one when I kept agar plates with bacteria’s in my closet at your house… It brings me so much happiness to hear my children talk about “our Americans”. You are all very special to me!

Melina – min glada, omtänksamma och smarta dotter. Du är orädd, vacker och rolig. Du vill och du gör. Du lyssnar och funderar. Du ger kärlek, värme och teckningar. Ditt hjärta är så stort, så stort. Min stolthet och glädje. Du kom till slut! Min älskade skatt. Du är den mest självklara jag vet. Tänk att just du vill hålla min hand!

Emelie – min genomkloka, empatiska och vackra dotter. Du är modig och snäll. Du berättar om livet, du frågar och du analyserar. Du är en härlig kämpe, fylld med värme! Du skrattar åt mina skämt (även när ingen annan gör det) och kramar mig när jag behöver det. Tänk att du är min (och har min prick), älskade barn. Men du är tydligt allra mest din egen! Stolt mamma är jag.

Anders – mitt lugn, min hjälp-kompass och mitt mysterium. Ibland min motsats, men alltid min trygghet. Du får mig att tänka och skratta, och att bara vara. Du räddar de 30 %, som 70 % -jag tappar bort. Det vackraste jag vet är att lyssna på samtal mellan dig och barnen. Tänk att du fanns ändå!

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